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Turkish Adaptation of the Mental Health Literacy Scale for Healthcare Students: A Study of Validity and Reliability

ABSTRACT

Objective: This study has aimed to investigate the validity and reliability of the Turkish version of the Mental Health Literacy in Healthcare Students (MHLS-HS).

Methods: The study sample comprises 275 students at Istanbul Medical Faculty between the ages of 18 and 27. Data were collected using the MHLS-HS, the Beliefs about Mental Illness Scale (BMI), and the Positive Mental Health Scale (PMS). For language adaptation, translation, back translation, expert comments, and a trial application were conducted. Validity was determined using the content validity index and confirmatory factor analysis, while reliability was determined using Cronbach's alpha analysis and the test-retest method.

Results: The content validity index of the scale was found to be 0.99 and the item loads were found to be 0.38-0.94 according to confirmatory factor analysis. The Cronbach's alpha coefficient was found to be 0.79 for the whole scale and between 0.60-0.89 for the five sub-dimensions. In equivalent criterion validity, it was determined that BMI had a weak negative correlation ($r=-0.360$, $p<0.001$) and a weak positive correlation ($r=0.327$, $p<0.001$) with PMS. A statistically significant difference was found in the sub-dimensions of Maintaining Positive Mental Health, Stigmatizing Mental Illnesses, and Seeking Help Effectiveness between those with and without mental illness in the discrimination analysis of the RSS-SS scale ($p<0.001$, $p=0.029$, $p=0.034$, respectively).

Conclusions: The Mental Health Literacy Scale in Healthcare Students was found to be valid and reliable. It can be used to assess and improve the educational experience of medical school students.

Keywords: Mental Health Literacy, Validity, Reliability, Healthcare Students, Scale.

Sağlık Öğrencileri İçin Ruh Sağlığı Okuryazarlık Ölçeğinin Türkçeye Uyarlanması: Geçerlik ve Güvenirlik Çalışması

ÖZET

Amaç: Bu çalışmada, Sağlık Öğrencileri için Ruh Sağlığı Okuryazarlık Ölçeğinin (RSOÖ-SÖ) Türkçe uyarlaması için geçerlilik ve güvenilirlik yapılması amaçlanmıştır.

Gereç ve Yöntem: Çalışma örneklemi 18-27 yaş arasında İstanbul Tıp Fakültesinde öğrenim gören 275 kişiden oluşmaktadır. RSOÖ-SÖ ölçeği, Ruhsal Hastalıklara Yönelik İnanç Ölçeği (RHYİÖ) ve Pozitif Mental Sağlık Ölçeğini (PMSÖ) veri toplamada kullanılmıştır. Dil uyarlaması için çeviri, geri çeviri, uzman görüşleri ve pilot uygulama yapılmıştır. Geçerlik için kapsam geçerlilik indeksi, doğrulayıcı faktör analizi ve güvenilirliği test etmek için Cronbach alfa analizi, test-tekrar test yöntemi kullanılmıştır.

Bulgular: Ölçeğin kapsam geçerlilik indeksi 0.99 ve doğrulayıcı faktör analizine göre madde yükleri 0.38-0.94 olduğu bulunmuştur. Cronbach alfa katsayısı tüm ölçek için 0.79, beş alt boyutu için ise 0.60-0.89 arasında olduğu belirlenmiştir. Eşdeğer ölçüt geçerliliğinde RHYİÖ ile negatif yönlü zayıf korelasyon ($r=-0.360$, $p<0.001$), PMSÖ ile ise pozitif yönlü zayıf korelasyon ($r=0.327$, $p<0.001$) gösterdiği saptanmıştır. RSOÖ-SÖ ölçeğinin ayırt edicilik analizinde ruhsal hastalığı olan ve olmayanlar arasında Pozitif Ruh Sağlığını Sürdürme, Ruhsal Hastalıkları Damgalama ve Yardım arama etkinliği alt boyutlarında istatistiksel olarak anlamlı fark saptanmıştır (Sırasıyla $p<0.001$, $p=0.029$,$p=0.034$).

Sonuç: Sağlık Öğrencileri için Ruh Sağlığı Okuryazarlığı Ölçeğinin geçerli ve güvenilir olduğu saptanmıştır. Tıp fakültesi öğrencilerinde eğitimin değerlendirilmesi ve iyileştirilmesi için kullanılabilir.

Anahtar Kelimeler: Ruh Sağlığı Okuryazarlığı, Geçerlik, Güvenirlik, Sağlık Öğrencileri, Ölçek.

INTRODUCTION

The World Health Organization (WHO) describes mental health as "a condition of well-being that an individual recognizes his or her strengths, can handle the usual demands of life, might work effectively, and also can make a significant contribution to his or her society"(1). Worldwide, an approximated 322 million individuals suffer from depression, 264 million from anxiety, 45 million from bipolar illness, 20 million from schizophrenia, and 50 million from dementia (2,3). More than 70% of these people are unable to get help from health professionals as they avoid and delay treatment due to a lack of knowledge to define mental illness, being unaware of how to access treatment, prejudice towards those with mental illness and fear of stigmatization (4,5).

Mental health literacy is a significant factor in mental health and has the order to enhance public mental health. (6). Studies have reported that knowing mental health and diseases increases one's awareness in seeking help and treatment, benefiting from health services and early diagnosis and reducing mental illness stigma in society (7,8) Several scales such as the Vignette Interview, the Mental Health Literacy Scale (MHLS), and the Mental Health Literacy Scale for Youth and Young Adults (MHLq) have been developed to determine one's mental health literacy (9-12). These scales were created to measure and examine the literacy levels of the public, but various studies have shown that mental health literacy should also be improved in healthcare professionals and students (medical school students, nursing students, health vocational school students, etc.) (13). Healthcare professionals and students have high levels of stress, burnout, anxiety and depression (14,15). Healthcare professionals and students exhibit a pervasive stigma, as well as unfavourable attitudes and beliefs, toward those with mental illness. Therefore, healthcare professionals and students may refuse to explain and ignore their mental problems and avoid seeking help and treatment (16,17). In addition, studies have reported that mental illnesses can be overlooked in primary care centres, whereby their diagnosis rates are low (18,19).

Previous studies have suggested identifying and improving mental health literacy among healthcare professionals and students. However, there is no Turkish scale to determine mental health literacy for healthcare students. Mental Health Literacy Scale for Healthcare Students, which covers five essential components of health literacy (maintaining healthy mental health, recognizing mental illness, a stigma attitude, help-seeking efficacy, and help-seeking attitude), may fill this gap (13). This study aimed to adapt the Mental Health Literacy Scale for Healthcare Students into Turkish and to determine its Turkish validity and reliability.

MATERIAL AND METHODS

Study Design and Sample Size: This methodological study was undertaken with healthcare students aged 18 to 27 who studied at the Istanbul University Faculty of Medicine during the educational year 2021-2022 and volunteered to participate. The data were collected online between November 2021 and March 2022. Filling out the questionnaire lasted around 20 minutes. The sample size in scale adaptation studies should be at least 5-10 times the number of scale items. Therefore, a total of 275 people were reached in this study (the number of scale items = 26) (20). Two weeks after the first phase of data collection, the questionnaire was sent again for re-testing to health students who already filled out it, and a total of 104 healthcare students responded. Ethical approval was received by the Social and Humane Ethics Committee (Dated: 30/03/2021 E-155284) at Istanbul University, and permission from Yin-Ju Lien, the co-author of the article, via e-mail, to use and verify the validity and reliability of the scale in Turkish (February 26, 2021).

Data Collection Tools: The data were gathered using a personal information form that included questions on healthcare students' sociodemographic characteristics of healthcare students and the Mental Health Literacy Scale for Healthcare Students (MHLS-HS). The data collection form included two additional scales, namely Positive Mental Health Scale (PMSÖ) and the Beliefs toward Mental Illness Scale (RHYİÖ), to examine the equivalent criterion validity of the scale.

The Mental Health Literacy Scale for Healthcare Students (MHLS-HS): The MHLS-HS was designed by Chao et al. utilizing a total of 1294 medical and public health undergraduate students from 11 universities to assess mental health literacy among healthcare students (13). It consists of 26 items and five 5 subscales (M = Maintenance of positive mental health 10 items; R = Recognition of mental illness 4 items; S = Mental illness stigma attitude 6 items; HE = Help-seeking efficacy 3 items; HA = Help-seeking attitude 3 items). This is a 5-point Likert type scale, scoring from 1 (strongly disagree) to 5 (strongly agree). The scale is interpreted through total and subscale scores, where the subscale of "S= Mental illness stigma attitude" is scored in reverse. A higher score indicates better mental health literacy. The MHLS-HS has good reliability. The Cronbach's alpha coefficient for the whole scale was 0.81 and varied from 0.70 to 0.87 for its subscales. The correlation of the MHL-HS with the Social Distance Scale and the Positive Mental Health Scale, which were used to achieve similar scale validity, supported the convergent validity of the MHL-HS, and higher MHL-HS total scores were significantly associated with lower social distance toward people with

mental illness (r = -0.26, respectively; $p < 0.001$, r = 0.35; $p < 0.001$) (13).

Positive Mental Health Scale (PMSÖ): Positive Mental Health Scale (PMHS) was developed by Lukat et al. (2016) and adapted into Turkish by Yılmaz-Akbaba and Eldeleklioğlu (2019) (21,22). It consists of nine items, scoring from "Not True (1) to "True (4)". The internal consistency coefficient of the PMSÖ was determined to be 0.85, and substantial positive connections were established between the PMSÖ and the scales used for similar scale validity.

Beliefs toward Mental Illness Scale (RHYİÖ): The Beliefs towards Mental Illness Scale (BMI) was created by Hirai and Clum (2000) and adapted into Turkish by Bilge and Çam (2008) (23,24). This is a 6-point Likert-type scale, scoring from "Totally Disagree (0)" to "Totally Agree (5)". It consists of 21 items and three subscales, involving danger, lack of social and interpersonal skills, and incurability. The Cronbach's alpha coefficient was 0.82 for the entire scale and ranged from 0.69 to 0.80 for the subscales.

Translation of the Scale and a Pilot Application: The steps of translation, back-translation and pilot application were followed sequentially to create the Turkish form of the scale. A professional translator who graduated in English language literature (C.B.) translated the scale from English to Turkish. A foreign citizen whose mother tongue is English and who speaks Turkish (K.Y.) translated it back from Turkish to English.

Upon the consensus of the researchers, the scale items were evaluated and scored by a total of seven experts, including six physicians and one psychiatric nurse, in terms of their accuracy, suitability and intelligibility for health students (M.Ç., A.M., L.B.A, S.U.U., E.Ç.K., Ü.Z., G.A.M.). Davis method was used to assess items on the scale, scoring "inappropriate (1)", "should be seriously reviewed (2)", "should be slightly revised (3)", and "appropriate (4)" (25). The content validity ratio (CVR) of the scale items ranged from 0.86 to 1.00, and the content validity index (CGI) was calculated to be 0.99.

A pilot application was conducted with a group of 30 healthcare students to evaluate the intelligibility of the scale. The data obtained from the pilot application were not used in the study.

Data Analysis: Before the analysis, the presence of missing data in the data set was checked (even though the scale was set in a way that respondents could not answer the next question without answering the previous one, thus the possibility of missing data was eliminated). The Kolmogorov-Smirnov test was utilized to determine whether or not the data has a normal distribution. The distribution of the data was not normal. As the data lacked a normal distribution, the Mann Whitney U test and Spearman's correlation analysis were applied for statistical analysis. The internal consistency and reliability of the scale and its subscales were evaluated using Cronbach's alpha. Correlation analysis and Interclass Correlation (ICC) analysis were used to compare the test-retest scale scores for time invariance. The construct validity of the scale was determined using confirmatory factor analysis (CFA). Davis method was used to calculate the CGI and CVR values, where the limit values for CVR and CGI should be above 0.80 and 0.67, respectively (25). PMSÖ and RHYİÖ were used for the convergent and discriminant validity of the scale. A p-value less than 0.05 was considered statistically significant. On the scale, items with reverse scores were scored in reverse. The IBM SPSS (Social Sciences Statistical Package) 20 package program, AMOS and Lisrel program were used to examine the data.

RESULTS

Characteristics of the Participants: The mean age of 275 healthcare students who agreed to participate in the study was 20.9±2.1 years (range, 18-27), 59.3% of them were women. In addition, 26.5% of them (n=73) were 1st graders, 19.6% (n=54) 2nd graders, 12.4% (n=34) 3rd graders, 7.6% (n=21) were 4th graders, 16.4% (n=45) were 5th graders and 17.5% (n=48) were 6th graders, 9.5% (n=26) they had chronic health issues, and 14.9% (n=41) had mental illness in the past.

Validity Analysis of the Mental Health Literacy Scale for Healthcare Students (RSOÖ-SÖ):

Content Validity: The scale was evaluated for content validity by seven field experts (M.Ç., A.M., L.B.A, S.U.U., E.Ç.K., Ü.Z., G.A.M.). The content validity ratio (CVR) of the scale items ranged between 0.86 and 1.00, and the content validity index (CGI) of the scale was determined as 0.99.

Construct Validity: A confirmatory factor analysis (CFA) was performed for the construct validity of the RSOÖ-SÖ. As a result, an item (numbered 4) in the subscale of "Maintenance of Positive Mental Health (M)", stating "*having religious or spiritual beliefs*", had a factor loading as 0.07, and an item (numbered 3) in the subscale of "Recognition of Mental Illness (R)", stating "*if one needs higher doses of a drug to achieve the same effect; to what extent do you think he/she is likely to have a substance-related addiction?*", had factor loading as 0.20. These two items were excluded from the scale due to low factor loadings. The CFA was conducted over 24 items and 5 subscales. CFA fit indices of the scale were as follows: χ^2/df 1.46, Root mean square error of approximation (RMSEA) = 0.041, Comparative fit index (CFI) = 0.96, Incremental fit index (IFI) = 0.96, Non-normed fit index (NNFI) = 0.95, Goodness-of-fit index (GFI) = 0.90, Standardized root mean square residual (SRMR)= 0.056, and Critical N (CN) = 219.37. Factor loadings of the scale items ranged between 0.38 and 0.94. Figure 1 shows the confirmatory factor analysis of the scale.

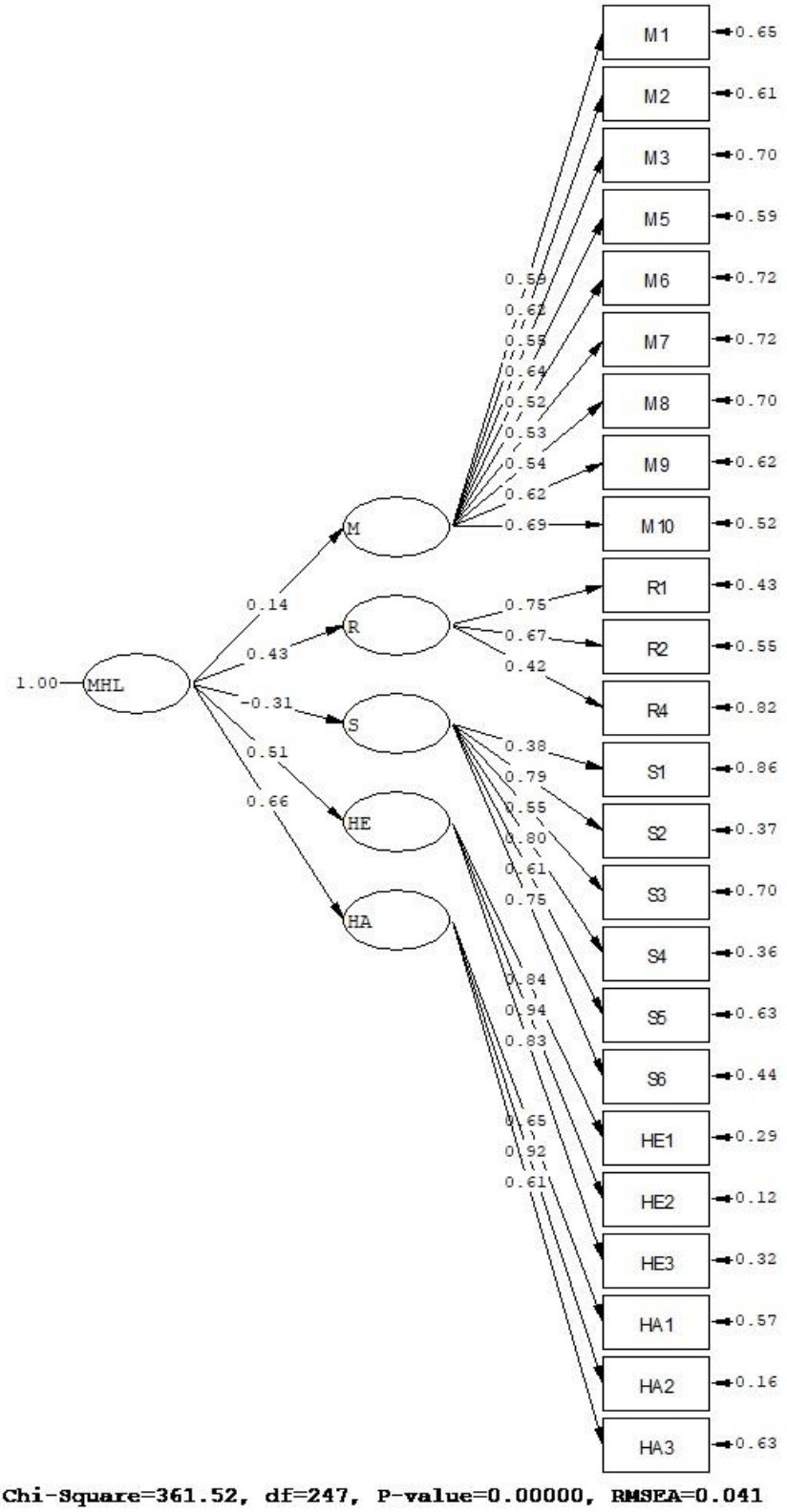

Figure 1. Confirmatory factor analysis diagram of the Mental Health Literacy scale for Healthcare Students

Equivalence Validity of the RSOÖ-SÖ: For the equivalence validity of the Mental Health Literacy Scale for Healthcare Students, its correlation with RHYİÖ and PMSÖ was evaluated, whereby the RSOÖ-SÖ had a weak negative correlation with RHYİÖ (r=-0.360, p<0.001) and a weak positive correlation with PMSÖ (r=0.327, p<0.001) (Table 1).

Differential Validity of the RSOÖ-SÖ: Table 2 compares the RSOÖ-SÖ and subscales scores of healthcare students according to the presence of mental illness.

Table 1. The correlation coefficients of the Beliefs towards Mental Illness Scale and the Positive Mental Health Scale of the RSOÖ-SÖ Scale and its sub-dimensions

	RHYİÖ	PMSÖ
MHLS-HS	-0.360**	0.327**
M	-0.028	0.125
R	-0.102	0.395**
S	-0.620**	-0.404**
HE	-0.114	0.651**
HA	-0.200**	0.523**

M = Maintenance of positive mental health R = Recognition of mental illness; Mental illness stigma attitude; HE = Help-seeking efficacy; HA = Help-seeking attitude; RHYİÖ= Beliefs towards Mental Illness Scale; PMSÖ = Positive Mental Health Scale ** p<0.001.

Table 2. Comparison of the RSOÖ-SÖ Scale and sub-dimension scores of the students according to the presence of mental illness

	Mental illness		
	None (n=234)	**Yes (n=41)**	**p**
M, median (1Q-3Q)	33(29-36)	28(24-32)	**<0.001**
R, median (1Q-3Q)	12(11-14)	13(12-14)	0.371
S, median (1Q-3Q)	21(19-24)	23(20-26.5)	**0.029**
HE, median (1Q-3Q)	12(9-14)	12(10.5-15)	**0.034**
HA, median (1Q-3Q)	10(8-12)	12(9-14)	0.070
MHLS-HS, mean±sd	88(80-94.3)	88(79-94)	0.837

M = Maintenance of positive mental health R = Recognition of mental illness; Mental illness stigma attitude; HE = Help-seeking efficacy; HA = Help-seeking attitude

Reliability Analysis of the RSOÖ-SÖ:

Internal Consistency Analysis of the RSOÖ-SÖ: The Cronbach's alpha reliability coefficient was found to be 0.796 for the total scale and ranged between 0.608 and 0.899 for its five subscales (Table 3). The item-total correlations were weak, moderate and positive (r=0.241-0.517). The correlation between the total scale and subscales scores ranged between 0.348 and 0.676 (p<0.001) (Table 4).

Table 3. The item score averages, factor loadings and internal consistency reliability

Sub-Dimensions	**Items**	**Median (1Q-3Q)**	**Factor Loadings**	**Cronbach's alpha**
M	M1	4(3-4)	0.59	0.826
	M2	4(3-4)	0.62	
	M3	4(3-4)	0.55	
	M5	4(3-5)	0.64	
	M6	4(2-5)	0.52	
	M7	4(3-4)	0.53	
	M8	4(3-4)	0.54	
	M9	3(2-4)	0.62	
	M10	3(2-4)	0.69	
R	R1	3(3-4)	0.75	0.608
	R2	4(4-5)	0.67	
	R4	4(4-5)	0.42	
S	S1	4(3-5)	0.38	0.810
	S2	1(1-2)	0.79	
	S3	2(1-3)	0.55	
	S4	3(3-4)	0.80	
	S5	2(2-3)	0.61	
	S6	3(2-4)	0.75	
HE	HE1	2(1-2)	0.84	0.899
	HE2	4(3-4)	0.94	
	HE3	4(3-5)	0.83	
HA	HA1	4(3-5)	0.65	0.758
	HA2	4(3-5)	0.92	
	HA3	3(3-4)	0.61	
RSOÖ-SÖ score		88(80-94)		0.796

Table 4. Correlation coefficients of the scores of the RSOÖ-SÖ Scale and its sub-dimensions

Sub- dimensions	M	R	S	HE	HA
R	0.081	-	-	-	-
S	0.043	0.130*	-	-	-
HE	0.114	0.233**	0.085	-	-
HA	0.088	0.226**	0.211**	0.326**	-
MHLS-HS	0.676**	0.348**	0.504**	0.532**	0.548**

M = Maintenance of positive mental health R = Recognition of mental illness; Mental illness stigma attitude; HE = Help-seeking efficacy; HA = Help-seeking attitude; p<0.05, ** p<0.001.

Test-Retest Reliability of the RSOÖ-SÖ: Two weeks later, the scale was reapplied to a total of 104 participants (50.5% (n=52) male) and the intragroup correlation coefficient (ICC) was calculated. The ICC was 0.894 for the total scale score (CI: 0.844-0.929). The total score correlation was found to be positive and very strong (r=0.875, p<0.001).

DISCUSSION

Mental health literacy is crucial to understanding how to improve and sustain positive mental health, identifying mental illnesses and treatment options, minimizing the drip of various psychiatric, increasing help-seeking efficacy and developing self-management skills, and is associated with the events frequently encountered in the course of a lifetime. This study examined the validity and reliability of the Mental Health Literacy Scale for Healthcare Students (MHLS-HS) in Turkish culture.

Discussion of Validity Analysis: A confirmatory factor analysis, which is an effective tool in assessing whether the factor model in the original scale is compatible with the data of the study was conducted to measure the construct validity of the scale (26). As a result, an item (numbered 4) in the subscale of "Maintenance of Positive Mental Health (M)" and an item (numbered 3) in the subscale of "Recognition of Mental Illness (R)" was excluded from the scale due to low factor loadings (0.07 and 0.20, respectively). Therefore, the subscale of Maintenance of Positive Mental Health included nine items, the subscale of Recognition of Mental Illness included three items, and the number of items in other subscales did not change. The factor loadings of the scale's last 24 items varied from 0.38 to 0.94. The factor loadings of scale items may vary by study. The factor loadings of the items in the scale were determined as 0.45 and above by Büyüköztürk et al. (27) and between 0.32-0.44 by Dede and Yaman (28). In our research, just two scale items had factor loadings of 0.38 and 0.42, while the remaining items had acceptable, very good, and excellent factor loading fit. Chao et al. found that the factor loadings ranged from 0.41 to 0.95(13). The CFA analysis revealed $\chi 2/df = 1.46$, RMSEA=0.041, IFI=0.96, CFI=0.96, GFI= 0.90, and SRMR=0.056, where $\chi 2/df \leq 3$, RMSEA $\leq$ 0.05, IFI $\geq$ 0.95 and GFI $\geq$ 0.90 indicated good fit of the scale and CFI $\geq$ 0.95 and SRMR $\leq$ 0.08 indicated acceptable fit of the scale (29). Therefore, the CFA and goodness-of-fit statistics of the scale items in our study were good and at the desired level.

For equivalent criterion validity of the scale, its correlation with RHYİÖ was analyzed and a weak negative correlation was identified between them (r=-0.360, p<0.001). A high score on the RHYİÖ indicates a negative belief (24). Therefore, we can conclude that as the mental health literacy of health students increases, their negative attitudes towards mental illness decrease. In addition, for the equivalent criterion validity of the scale, its correlation with PMSÖ was also evaluated and a weak positive correlation was identified between them (r=0.327, p<0.001). A high PMSÖ score suggests great positive mental health. (22). Help-seeking efficacy and help-seeking attitude, two subscales of the RSOÖ-SÖ, showed higher correlations with the PMSÖ (0.651 p<0.001 and 0.523 p<0.001, respectively). Chao et al. (13) found a low positive correlation between the scale and the PMSÖ (r=0.35 p < 0.001).

Discussion of Reliability Analysis: The item-total score correlations of 24 items were positive, weak and moderate (r=0.241-0.517). The correlation coefficient between the overall scale and the five subscales ranged from 0.348 to 0.676. Positively significant relationships between the whole scale and subscale scores were obtained (p<0.001). This consequence theoretically coincides with the fact that as the mental health literacy level of healthcare students increases, they are willing to expand their knowledge about achieving and sustaining excellent mental health, their awareness of mental disorders and treatments, and their attitudes toward stigma reduction and help-seeking effectiveness.

The overall scale's Cronbach's alpha reliability coefficient (α) was determined to be 0.79 and ranged between 0.60 and 0.89 for its subscales, where $0.60 \leq \alpha \leq 0.80$ indicates that the scale is quite reliable (30). According to Chao et al., Cronbach's alpha coefficient was 0.81 for the entire scale and 0.70-0.87 for its subscales (13). Accordingly, our results comply with those reported by Chao et al.(14). In the adaptation study of the Mental Health Literacy Scale (MHL) to young adults (MHL-q), Cronbach's alpha was found to be 0.84 for the overall scale and 0.60 to 0.74 for the subscales. However, the items (29 items) and subscales (4

subscales) of the MHL-q are quite different from those in our scale (12).

The scale was re-applied two weeks later to assess its time consistency, and its first and second application scores were found to have a strong and positive correlation (r=0.875, p<0.001). An ICC analysis was performed to evaluate the agreement between test and retest scores of the scale, which was determined to have statistical significance (p<0.001). Thus, the scale was found to have test-retest reliability.

Discussion on the Relationship between Descriptive Characteristics and Subscales of the Scale: The healthcare students with mental illness had lower scores on the subscales of maintaining psychological wellbeing, mental disease stigma attitude, and higher scores on the subscale of help-seeking efficacy than those without mental illness, and the difference between them was statistically significant (respectively <0.001, 0.029, 0.034). Studies have indicated that persons with greater mental health literacy have better mental health and a less social distance from those with mental illness (30,31).

Items on the subscale of Maintenance Positive Mental Health subscale (M) of the RSOÖ-SÖ include items to positively affect competence, autonomy and mental health. Studies have reported that meeting these basic psychological needs leads to a better quality of life and mental health (32). Therefore, healthcare students, who will become health professionals in the future, should be provided with better mental health and better patient care (33).

The subscale of Recognition of Mental Illnesses (R) of the RSOÖ-SÖ includes items to identify mental illnesses such as schizophrenia, anxiety disorders, depression etc. Several mental disorders are common both in Turkey (34) and across the world (18). Increasing the knowledge of healthcare students on recognition of mental illness is important for early diagnosis and treatment when they graduate and start providing health services.

Another subscale of the RSOÖ-SÖ is the mental illness stigma attitude. Jorm and Kitchener have found that mental health literacy interventions and knowledge about mental illnesses reduce stigma (35). Link and Phelan explained that recognition of mental illness and labelling can have both positive and negative aspects, where labelling other persons can be stigmatizing and labelling oneself can be a facilitator in treatment (36). If healthcare students can easily recognize mental illnesses and avoid labelling and stigmatization, they can accelerate patients' recovery. Discriminating tendencies of healthcare students can be detected using the scale and relevant educational interventions can be applied to them (13).

Strengths and Limitations: According to our knowledge, the RSO-S is the first instrument particularly created to measure mental health literacy among students in the healthcare field. Public healthcare students participated in the study of the original scale, but this study was conducted only with medical faculty students. However, there are no public healthcare students in undergraduate education in Turkey as the public health speciality is considered a separate branch after medical school. Therefore, we did not include public health assistants to avoid bias in the sample selection. In addition, our study does not represent all healthcare students in Turkey as it was conducted in a single faculty. Further studies can use different healthcare student groups and can be performed in multi-centred faculties. This is a self-report scale, therefore, even though invisibility and clandestinity are ensured during the study, the measurement of stigmatization towards mental health may not be completely independent of social desirability bias.

CONCLUSION

Our research suggests that the Turkish version of the RSOÖ-SÖ is a valid and reliable instrument with an adequate model fit. The RSOÖ-SÖ captured the multidimensionality appropriately, and the analysis confirmed the suitability of its five-factor structure. This scale encompasses both mental health promotion and many dimensions of mental health, including stigma and awareness of the mental illness. It allows rapid and comprehensive evaluation of mental health literacy among healthcare students and to conduct remedial curriculum studies in medical schools.

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RESEARCH ARTICLE

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Evaluation of Simulation-Based Educational Approaches in Family Medicine Specialization Education

ABSTRACT

Objective: The purpose of our activity is to increase the skill levels of Family Medicine assistants in the interventional competencies including in the TUKMOS (Medical Specialization Board Curriculum Formation and Standard Setting System) Family Medicine specialization education curriculum by using the facilities in our simulation center.

Methods: We carried out the 'RSIM 1. Family Medicine Assistants Simulation Education project, which we planned in line with the TUBITAK-BIDEP 2237 Support Program with the participation of a total of 32 Family Medicine assistants. Education pretest-posttest was applied to all participants. In addition, a simulation education feedback survey consisting of 34 questions was conducted.

Results: 71.9% (n:23) of the participants in the education were women, and 56.2% (n:18) have been working in a university hospital. Those with an active working period of fewer than 2 years in medicine were 59.4% (n: 19), and those with the assistantship period of 2-3 years were 53.1% (n: 17). When the pre-test and post-test mean scores of the participants were compared, the difference was found to be statistically significant ($p<0.001$).

Conclusions: The post-test score was higher than the pre-test in each group categorized by gender, type of institution, year of work, and duration of the assistantship. In the light of this finding, we can say that the education provided achieved its purpose in all groups. We think that simulation training is effective, useful, and necessary due to the positive results we have achieved as a result of the practical application we have carried out.

Keywords: Simulation-Based Education, Family Medicine, Medical Education.

Aile Hekimliği Uzmanlık Eğitiminde Simülasyon Temelli Eğitim Yaklaşımlarının Değerlendirilmesi

ÖZET

Amaç: Etkinliğimizin amacı TUKMOS (Tıpta Uzmanlık Kurulu Müfredat Oluşturma ve Standart Belirleme Sistemi) Aile Hekimliği uzmanlık eğitimi müfredatında yer alan girişimsel yetkinlikleri simülasyon merkezimizdeki imkanlar kullanılarak Aile Hekimliği Asistanlarına sunularak beceri düzeylerinin arttırılmasıdır.

Gereç ve Yöntem: TÜBİTAK-BİDEP 2237 Destekleme Programı doğrultusunda planladığımız 'RSİM 1. Aile Hekimliği Asistanları Simülasyon Eğitimi' projesini toplam 32 Aile Hekimi asistanın katılımıyla gerçekleştirdik. Tüm katılımcılara eğitim ön test-son test uygulandı. Ayrıca 34 sorudan oluşan simülasyon eğitimi geri bildirim anketi yapılmıştır.

Bulgular: Eğitime katılanların %71,9'u (n:23) kadın, %56,2'si (n:18) üniversite hastanesinde çalışmaktaydı. Hekimlikte geçen aktif çalışma süresi 2 yıldan az olanlar %59,4 (n:19), asistanlık eğitim süresi 2-3 yıl olanlar %53,1 (n:17) idi. Katılımcıların ön test ve son test ortalama puanları karşılaştırıldığında arasındaki fark istatistiksel olarak anlamlı bulundu ($p<0,001$).

Sonuç: Yapılan son test puanı cinsiyet, çalışılan kurum tipi, çalışma yılı süresi ve asistanlık eğitim süresine göre kategorize edilen her grupta ön teste göre daha yüksekti. Bu bulgu ışığında verilen eğitimin bütün gruplarda amacına ulaştığını söyleyebiliriz. Gerçekleştirdiğimiz pratik uygulamanın sonuçlarından elde ettiğimiz olumlu sonuçlar nedeniyle simülasyon eğitiminin etkili, yararlı ve ihtiyaç olduğunu düşünmekteyiz.

Anahtar Kelimeler: Simülasyon Temelli Eğitim, Aile Hekimliği, Tıp Eğitimi.

INTRODUCTION

Simulation, which means imitating the tasks, relationships, behaviors, or some cognitive activities that exist in reality, is nowadays used in many fields from engineering to medicine, from the aviation industry to the defense industry (1). The use of simulation in the field of medicine is based on the 1950s (2). Its development in medicine has been with Ressü-Anni which is a common product of industrial engineering and medical science, in the 20th century (2). The simulator must be able to comply with the actions of the participant. The more these features are in the simulation system, the more the participants can transfer what they have learned to real situations (1,3).

Simulation-based education gives every student a chance to learn, provides equality, allows different learning methods, and ensures the effective use of adult learning principles (1,4-7). For this reason, the need for simulation-based education in medical education is increasingly growing. But the environment and educational materials needed for this method of education are very costly. At the same time, it is necessary to make the correct programming to carry out this education. While we have the facilities of the Clinical Simulation Education Center within our faculty, we wanted to organize an event using these facilities. We realized our event by turning this into a Tübitak Project with appropriate programming.

Emergency room, intensive care unit, delivery room, operating room, Basic Skills laboratory, home health services room, standard patient room, Objective Structured Clinical Examination (OSCE) rooms, debriefing rooms, support areas (warehouse, technical area, etc.), and ambulance are available in the Recep Tayyip Erdoğan University Clinical Simulation Education Center (RSIM) and a complete hospital environment has been created with its physical structure. Here, pre-graduate and post-graduate education opportunities are provided to physicians. At RSIM, not only simulators but also virtual patient practices (Body-interact, Take the Winds, Portugal) contribute to education. In addition, the camera and sound recordings of all kinds of practices and initiatives made by the students are analyzed in the debriefing rooms by the simulation center management and operating system (Learning Space, CAE, USA). This method allows students to learn from their mistakes. It is aimed to provide education to students on topics such as communication with simulated/standardized patients, motivation, teamwork, and patient and employee safety in the OSCE (Objectively Structured Clinical Examination) rooms.

In the project we organized with the TUBITAK Scientist Support Programs Presidency (BIDEP) 2237 Scientific Education Activities Support Program, we aim to develop the basic principles, knowledge, skills, attitudes, and behaviors available in Family Medicine specialization education, as well as to provide appropriate opportunities for the development of health education, research, and management skills. Another aim of the study is to increase the skill levels of Family Medicine assistants in the interventional competencies (Basic Life Support, Advanced Cardiac Life Support, Obstetrics, Approach to Hypertension Patient with Simulated Patient, Approach to Febrile Convulsion and Case Reports with Virtual Patient) including in the TUKMOS (Medical Specialization Board Curriculum Formation and Standard Setting System) Family Medicine specialization education curriculum by using the facilities in our simulation center.

MATERIAL AND METHODS

Ethics committee approval for this study was taken from the Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine with protocol number 2022/163.

We carried out the 'RSIM 1. Family Medicine Assistants Simulation Education Project, which we planned in line with the TUBITAK-BIDEP 2237 Support Program for Scientific Educational Activities, on 26-27 November 2021 at the clinical simulation center of our faculty with the participation of a total of 32 Family Medicine assistants from different cities of Turkey. The assistants who will participate in this education were randomly selected from among the applications, paying attention to the conditions of 'to work as a full-time assistant in family medicine specialization education in a university or education and research hospital in any province of Turkey, to have a motivation letter written by the candidates who want to participate in the education, to be a family medicine assistant for at least 12 months '.

The training subjects in our project consisted of 6 topics such as Basic Life Support, Advanced Cardiac Life Support, Obstetrics, Approach to Hypertension patient with Simulated Patient, Approach to Febrile Convulsions, and Case Reports with Virtual Patient in Chest Diseases, which are among the interventional competencies included in the TUKMOS Family Medicine specialty education curriculum. The reason why these course subjects were chosen for the program is that they are among the subjects we need to diagnose, treat and manage the patient correctly in the family medicine specialty education curriculum. In addition, according to the TUKMOS Family Medicine curriculum, we need to have the ability to manage the whole process of the patient's diagnosis and treatment by working as a team on the approach to the pneumonia patient mentioned in Hypertension and Chest diseases.

For each lesson in the project program, firstly, theoretical lessons were lectured. After each

theoretical lesson, a practical application of that lesson was made to reinforce the subjects and increase their retention.

The educator had each participant apply basic life support practical training one by one. While the participant was performing the resuscitation, the adequacy of CPR was evaluated by looking at the amplitude and frequency of the compressions made on the computer, and the wrong practices were tried to be corrected.

Advanced cardiac life support practice was taught to each participant by the educator in groups of two, with patient management on the simulator as a team. The rhythm of the simulated patient was changed over the computer and they were asked to intervene in the patient. The content of these interventions was asystole intervention, CPR, ambulation, adrenaline administration, pulseless VT (ventricular tachycardia) intervention, and defibrillation.

In the practice of approach to the hypertension patient, each participant was compared by the educator with the simulated patient in the hypertensive patient role. Prior to this, the participants were given theoretical education based on the Turkish Hypertension Consensus Report. As the learning objectives, it was aimed that the participants should measure blood pressure in a hypertension patient, question the necessary anamnesis information, systemic examination, doctor-patient relationship, request necessary laboratory tests, explain lifestyle changes, and write the appropriate prescription and follow up. After the practice, the camera footage recorded in the OSCE rooms was watched and the debriefing session was started, and the necessary explanations were made by determining the knowledge and skill levels of the participants.

The practice of the birth lesson was carried out in pairs, in the birth simulator, under the supervision of the educator. The delivery of a term baby with the normal head presentation was performed on a simulated pregnant patient who had labor pains, reached adequate cervical dilation, and entered labor. First, the head of the baby was seen, after the head was removed, the shoulder was helped to come out by holding it, and then the whole baby was removed gradually. The cord was clamped after waiting for 30 seconds to 1 minute. The cord was gently pulled without pulling too much to assist the exit of the placenta. With the removal of the placenta, the normal birth step was completed.

In the febrile convulsion practical education, the participants were divided into groups of two and it was aimed to provide patient management with teamwork. It was requested to intervene in the child who had a fever and had a seizure by using the simulator. Changes were made to the clinical and symptoms of the simulated patient on the computer, according to the interventions made to the patient. The things to be expected from the participants in the first meeting with such a patient are as follows: taking a short anamnesis to explain the etiology quickly (from the simulated patient's relative), doing what needs to be done in the first 2 minutes (opening the airway, giving nasal oxygen, opening the vascular access), to have sufficient knowledge about other treatment options in the patient who could not establish vascular access (rectal diazepam administration), intervention to stop the seizure (oxygen support, cold application) and drugs (paracetamol, diazepam, midazolam, phenytoin).

The practice of the pulmonology step was covered by the educator with case reports on virtual patients with 'Body-interact'. It contributed to the participant's analysis of pneumonia in terms of diagnosis, treatment, and follow-up of the patient. 'Body-interact' is a virtual patient program in which 54 different cases are analyzed. In this program, the participant was able to monitor the patient's anamnesis information and request the necessary laboratory and imaging tests and intervene with the patient.

At the end of each practical lesson, the participant or participants who completed their practice were told what they did wrong during that practical application, and the mistakes made were explained and corrected. Debriefing was done by listening to the positive and negative criticisms, contributions, and ideas of the participants regarding the courses and practical applications.

All participants were asked 4 questions (24 questions in total) from each lesson in order to have an idea about the participant's knowledge about the lessons before the lessons in the project, and a pre-test consisting of 5 questions including demographic information was applied. Demographic information was as name surname, gender, the institution of assistantship, active working year in medicine, and active working month as an assistant. The questions in each topic were created by their own departments. The pre-test was completed at the same time by all the participants in one class. After all the education was completed, the post-test was administered to all participants by applying the same pre-test. After the final test, the data were evaluated and compared with each other. In addition, a simulation education feedback survey was conducted consisting of 34 questions including questions such as 'Were you satisfied with the education provided?, 'Which course did you benefit more from?', 'Does the simulated practices have a high instructive role?'

Statistical Analysis: SPSS 22.0 statistical package program was used in the analysis of the data. Descriptive statistics of the evaluation results are given as numbers and percentages for categorical variables, and as median, minimum, and maximum for numerical variables. Comparisons of numerical variables between two independent groups were evaluated with the Mann Whitney U

test, and comparisons of numerical variables between two dependent groups were evaluated with the Wilcoxon test. The statistical alpha significance level was accepted as p<0.05.

RESULTS

As part of the TUBITAK project, the simulation education we held at RSIM on 26-27 November was held with the participation of 32 family medicine assistants.

71.9% (n:23) of the participants were female and 28.1% (n:9) were male. While 56.2% (n: 18) have been working in the university hospital, 43.8% (n: 14) have been working in the education-research hospital. When the active working time in medicine was evaluated, it was 59.4% (n:19) for those who were fewer than 2 years, 25.0% (n:8) for those who were 2-3 years, and 15.6% (n:5) for those who were more than 4 years. When the duration of the assistantship of the participants was examined, 46.9% (n: 15) have been family medicine assistants for fewer than 2 years and 53.1% (n: 17) for 2-3 years (Table 1).

28.1% (n:9) of the 32 participants who participated in the simulation education held at RSIM had received any simulation education before, and 71.9% (n:23) had not participated in any simulation education before (Figure 1).

Table 1. Sociodemographic characteristics of the participants

Variables	n	%
Gender		
Female	23	71.9
Male	9	28.1
Institution which working at		
University Hospital	18	56.2
Education-Research Hospital	14	43.8
Year of Work		
< 2	19	59.4
2-3	8	25.0
≥ 4	5	15.6
Duration of The Assistantship		
≥ 1, <2	15	46.9
2-3	17	53.1
Status of Receiving Simulation Education Before		
Yes	9	28.1
No	23	71.9

The results obtained in the pre-test-final test study of a total of a 24-question questionnaire consisting of 6 sections and 4 questions applied to all participants are summarized in Table 2.

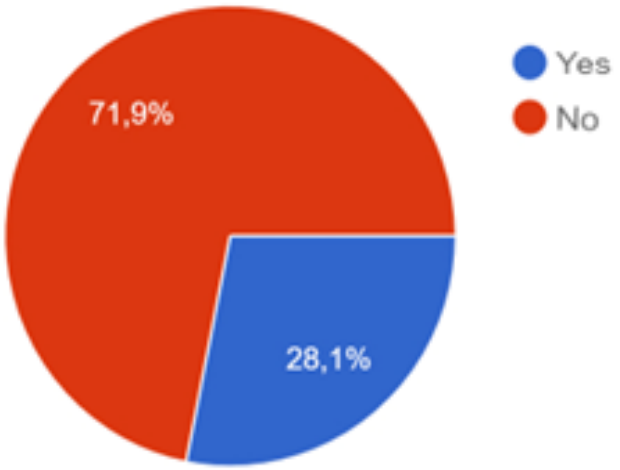

Figure 1. The previous simulation-based education status of the participants

Table 2. Participants' pre-test and post-test scores

	Pre-Test Avg (min-max)	Post-Test Avg (min-max)	p
Whole Group	11 (6-19)	22 (17-24)	<0.001
Gender			
Female	11 (6-16)	22 (17-24)	<0.001
Male	12 (9-19)	22 (17-24)	0.008
Institution which working at			
University Hospital	11 (7-19)	22 (17-24)	<0.001
Education-Research Hospital	11 (6-15)	20.5 (17-24)	0.001
Year of Work			
< 2	12 (6-19)	22 (17-24)	<0.001
≥ 2	10 (8-16)	22 (17-24)	0.001
Duration of The Assistantship			
≥ 1, <2	11 (7-19)	22 (17-24)	0.001
2-3	11 (6-16)	21 (17-24)	<0.001

When the pre-test and post-test mean scores of the participants were compared, the difference was found to be statistically significant ($p<0.001$).

The answers to the evaluation questions included in the satisfaction questionnaire conducted at the end of the education are shown in Table 3.

Table 3. Participants' satisfaction survey results

	5 points n (%)	4 points n (%)	3 points n (%)	2 points n (%)	1 point n (%)
Planned practical education with an educator facilitates the acquisition of new skills.	30 (93.8)	2 (6.3)	-	-	-
Simulation education should be a part of in-service education.	30 (93.8)	2 (6.3)	-	-	-
I think it is a good educational model to eliminate risks in terms of patient safety.	29 (90.6)	3 (9.4)	-	-	-
Simulation education contributed to the increase of my knowledge and skills.	29 (90.6)	3 (9.4)	-	-	-
I think that the clinical skill obtained through simulation-based education is an important skill that I will use in my professional life.	29 (90.6)	2 (6.3)	1 (3.1)	-	-
I think that simulation-based education is effective education for me to see and correct my deficiencies.	28 (87.5)	4 (12.5)	-	-	-
I think that the educational role of practices made through simulation is high.	28 (87.5)	4 (12.5)	-	-	-
The educator's feedback helped me understand the topic better.	28 (87.5)	3 (9.4)	1 (3.1)	-	-
The realism of the environment was effective in making the scenario more believable	58 (78.1)	7 (21.9)	-	-	-
I found the physiology of the simulator realistic	24 (77.4)	6 (18.8)	1 (3.1)	-	-
My expectation about the practice was met	23 (71.9)	6 (18.8)	3 (9.4)	-	-
I think simulation-based education is standardized education	23 (71.9)	4 (12.5)	3 (9.4)	2 (6.3)	-
I have seen that the equal knowledge and skill levels of the people in the team affect the success.	21 (65.6)	8 (25.0)	2 (6.3)	1 (3.1)	-
I think it makes me feel as a real environment in my attempts with the simulator.	19 (59.4)	10 (31.3)	2 (6.3)	-	1 (3.1)
Examples for the practice were sufficient	19 (59.4)	10 (31.3)	2 (6.3)	-	1 (3.1)
The RSIM environment made me feel like I was meeting a real hospital environment.	18 (56.3)	12 (37.5)	2 (6.3)	-	-
Practice time and equipment used were sufficient for crisis management skills	17 (53.1)	10 (31.3)	3 (9.4)	2 (6.3)	-
Seeing the mistakes made in the video recordings contributed to my learning.	17 (53.1)	8 (25.0)	7 (21.9)	-	-
Observing other participants during the education contributed to my learning.	16 (50.0)	11 (34.4)	5 (15.6)	-	-
The theoretical knowledge given on the subject was sufficient in terms of education.	14 (43.8)	11 (34.4)	6 (18.8)	1 (3.1)	-
I would like to make a preliminary evaluation by watching my practice footage again.	11 (34.4)	8 (25.0)	5 (15.6)	5 (15.6)	3 (9.4)
The fact that the practices are being recorded created stress for me.	6 (18.8)	10 (31.3)	5 (15.6)	4 (12.5)	7 (21.9)
During the education, I had difficulty remembering the theoretical information I knew.	6 (18.8)	6 (18.8)	8 (25.0)	9 (28.1)	3 (9.4)
The time allotted to education was sufficient.	3 (9.4)	9 (28.1)	10 (31.3)	6 (18.8)	4 (12.5)
Being in simulation education had a negative effect to show my real performance.	2 (6.3)	3 (9.4)	10 (31.3)	9 (28.1)	8 (25.0)

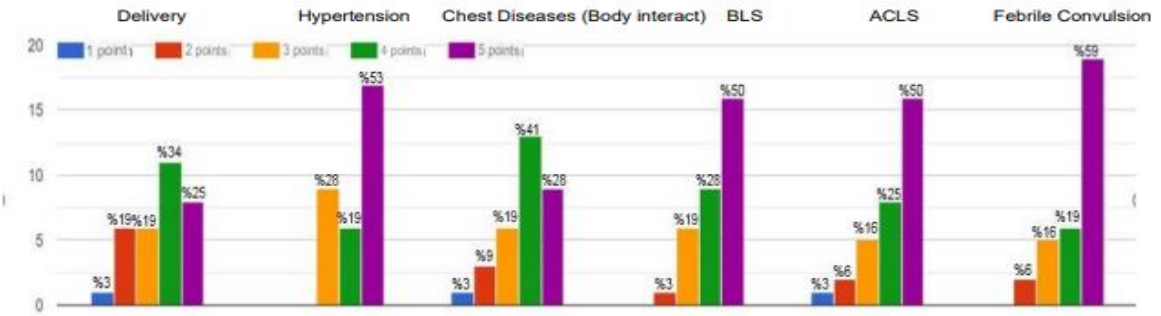

Figure 2. Participants' evaluations of the education parts

The points and course distributions of the answers to the question "Which practice has had the most permanent effect on your education?" in the satisfaction survey are as in Figure 2. The subject of the course with the highest score of 5 was febrile convulsions with 59%, while the subject of hypertension was in second place with 53%. With 25%, the birth course was in the last place.

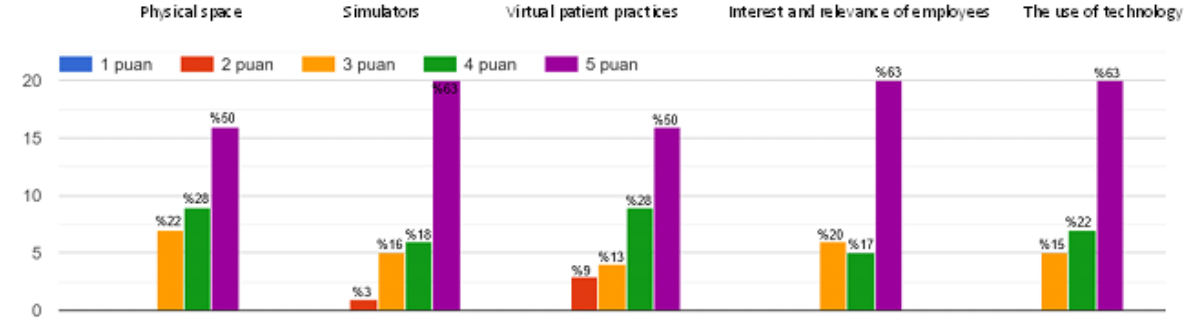

Figure 3. Evaluation of the possibilities of the simulation center

The answers to the question “What are the most impressive aspects of the Clinical Simulation Education Center?” in the satisfaction survey are shown in Figure 3. While the highest scorers with 63% were the use of technology, the interest and relevance of the employees, and the simulators, these were followed by physical space and virtual patient practices with 50% points.

DISCUSSION

Simulation-based medical education practices are innovative practices used in medical education. The increasing number of physicians and medical faculty students in recent years has caused problems in practical applications and inadequacies in education. In order to overcome these negativities, a need for simulation-based education has arisen. Simulation allows real-life events to be repeated in a safe environment, enabling students to improve their practice skills and learn about their failures. Thus, it is possible to improve students' practical skills with simulation-based education without putting the patients at risk (8).

The simulation laboratory provides different educational benefits to learn how to recognize and treat rare, complex clinical problems. The costs of simulator-based education programs include facilities, equipment, and personnel (9). R-SIM, which is within our faculty, includes these features. We have implemented a practice of simulation-based medical education with innovative learning methods and digital practices with family medicine assistants from different provinces of Turkey.

In our single-centered study with 32 people, we found a statistically significant difference between the pre-test applied to the participants before the simulation education and the post-test applied after the training ($p<0.001$). This research has shown that the use of simulation tools and education methods in specialization education after medical education can enable assistants to increase their learning qualities, improve their practice skills, and increase their level of knowledge on specialization issues.

When we examined the studies examining the relationship between the simulation education model and medical education in the literature, Issenberg et al. in a systematic analysis in which they examined simulation studies, revealed that simulation practices are tools that effectively support learning, provided that they are used in the right conditions and with appropriate methodology (10). According to Lammers et al., suitable conditions for an effective simulation education are integrating simulation practices into the education program, providing effective feedback to students during the learning experience, providing repetitive practice, increasing the difficulty level of the scenario or practice throughout the practice, keeping the educational environment under control, enabling individual learning, determining clear and measurable educational goals and outputs (11). In

our study, the pre-test mean score was 11, the post-test mean score was 22, and this difference between the tests was statistically significant ($p<0.001$). The design of our study was adjusted in accordance with the recommendations of Lammers et al. This difference between the two tests can be explained by the fact that the simulation education applied increases the knowledge and education levels of family medicine assistants compared to the pre-education period.

Studies investigating the relationship between the simulation education model and the specialization education of physicians are very limited in the literature. Okuda et al. stated that a remarkable improvement was observed in the team educated in the use of simulation in both vocational and academic emergency medicine education in a five-year emergency medicine education study (12). As far as we know, our study is the first to examine the relationship between family medicine specialization education and the simulation education model.

The post-test score was higher than the pre-test in each group categorized by gender, type of institution, year of work, and duration of the assistantship. In the light of this finding, we can say that the education provided achieved its purpose in all groups.

Simulation-based medical education is a complex service intervention that must be planned and implemented with attention to organizational contexts (13). The contributions of this form of education to the development of skills are seen as having the potential to provide a risk-free learning tool, reduce the number and effects of medical errors, facilitate open change in educational situations, increase patient safety and reduce dependency (14).

Family Medicine specialization education aims to provide opportunities suitable for the clinical knowledge, skills, attitudes, and behaviors of the assistants in line with the basic principles included in the definition of family medicine. Providing the interventional competencies included in the Family Medicine specialization education to the assistants through simulation education contributed to both patient safety and the skill level of the assistants.

The development and research of simulation-based medical education practices have grown and matured in recent years for important and methodological reasons (13). We think that simulation education is effective, useful, and a requirement due to the positive results we have obtained from the results of the practical application we have carried out.

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RESEARCH ARTICLE

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A Retrospective Study on Sexual Assault - Abuse Cases

ABSTRACT

Objective: In this study; it is aimed to analyze the sexual attack-abuse cases that occurred in Bolu province and were judged by the High Criminal Court.

Methods: A total of 148 cases of sexual assault - abuse decided by the Bolu High Criminal Court between 2007 and 2016 were analyzed retrospectively.

Results: This study included 148 cases: 131 (88.5%) cases were female and 17 (11.5%) were male. The mean age was 18.6 ± 11.6 (min:4, max:83). The highest number of cases was in the 13-15 age group (n=52, 35.2%). Sexual abuse most frequently occurred through vaginal penetration (n=72: 48.6%). The most common psychiatric diagnosis was acute stress disorder (n:12, 10.8%) and post-traumatic stress disorder (n:12, 10.8%). Physical violence was found to be statistically effective (p = 0.008) in the occurrence of mental disorders after the event. The victim recognized 81.8% of the attacker.

Conclusions: We think that more effective sexual attack-abuse prevention strategies can be developed at the national level by determining the risk factors of sexual assault-abuse in our country through wider research to be conducted across the country.

Keywords: Sexual Attack, Sexual Abuse, Victim, Attacker, Examination Findings.

Cinsel Saldırı – İstismar Olguları Üzerine Retrospektif Bir Araştırma

ÖZET

Amaç: Çalışmada; Bolu ilinde meydana gelen ve Ağır Ceza Mahkemesi'nde yargılaması yapılarak karara bağlanan cinsel saldırı - istismar olgularının analizi amaçlanmıştır.

Gereç ve Yöntem: 2007-2016 yılları arasında Bolu Ağır Ceza Mahkemesi'nde karara bağlanmış toplam 148 cinsel saldırı-istismar olgusu retrospektif olarak incelenmiştir.

Bulgular: Çalışmaya dahil edilen 148 olgunun 131'i (%88,5) kadın, 17'si (%11,5) erkektir. Ortalama yaş 18,6±11,6'dır (min:4, max:83). En fazla olgu %35,2 (n=52) oranı ile 13-15 yaş grubundaydı. Cinsel saldırı-istismar eyleminin en sık vajinal penetrasyon (n=72, %48,6) şeklinde gerçekleşmişti. En sık tespit edilen psikiyatrik hastalık akut stres bozukluğu (n=12, %10,8) ve travma sonrası stres bozukluğuydu (n=12, %10,8). Fiziksel şiddetin, olay sonrasında ruhsal bozukluk oluşmasında istatistiksel olarak etkili (p=0,008) olduğu bulundu. Saldırganların %81,8'i mağdur tarafından tanınıyordu.

Sonuç: Ülke genelinde yapılacak daha geniş çaplı araştırmalar ile ülkemizdeki cinsel saldırı-istismar risk faktörlerinin tespit edilerek, ulusal düzeyde daha etkili cinsel saldırı-istismar önleme stratejilerinin geliştirilebileceğini düşünüyoruz.

Anahtar Kelimeler: Cinsel saldırı, cinsel istismar, mağdur, saldırgan, muayene bulguları.

INTRODUCTION

Sexual crimes are among important social problems that threaten people of all age groups all over the world which can cause severe and permanent trauma to its victims, and its incidence has increased rapidly among violent crimes, especially in recent years (1,2). Sexual assault is a behavior that is not accepted by the society, aiming at the sexual satisfaction of the perpetrator by using coercion, such as physical force, threats, fear, cheating, and deception, against a woman or man whose consent is not accepted on legal grounds due to reasons such as underage or mental illness (3). Exposing a child or adolescent to activities aimed at sexual pleasure by using force, threats, or deception by adults in order to satisfy the sexual desires and needs of the aggressor is defined as child sexual abuse (4). Throughout the world, 19.7% of women and 7.9% of men are exposed to sexual abuse during childhood or adolescence (5). Although sexual assault, a rapidly increasing global problem in recent years, it is generally kept secret, and statistics do not reflect the actual situation. According to the data of the World Health Organization (WHO), one out of every five women in the world is exposed to sexual assault.

In addition, it has been stated that approximately 27% of women and 14% of men are exposed to sexual abuse in childhood and that one out of every three women all over the world is subjected to sexual violence (3). Since the trauma caused by sexual abuse in the genital areas, and subsequent neurobiological damages are more severely felt by the victim, the importance of performing comprehensive examinations of victims of abuse by experienced physicians is an undeniable fact. Considering the difference in punishments between sexual crimes; adequate, clear, and descriptive writing of forensic and medical reports and the acquisition, storage and transfer of appropriate material is of particular importance and requires care in eliminating grievances and inflicting the necessary punishment (1,6). In this study, it is aimed to retrospectively examine a total of 148 sexual assault-abuse cases resolved between the years 2007, and 2016 and to discuss the relevant data in the light of the literature.

MATERIAL AND METHODS

For the study, first of all, a data analysis form prepared for the purpose of the research was created. Since the study was planned as a retrospective review and the data that would disclose the identity information of the cases were not used, it was not necessary to create an informed consent form. Then, ethics committee approval dated October 17, 2016 and numbered 198 was obtained from Bolu Abant Izzet Baysal University Clinical Research Ethics Committee in order to carry out the study.

Subsequently, the files of sexual assault-abuse cases among the files that were resolved at the Bolu High Criminal Court between 01.01.2007 – 12.31.2016 were identified and examined retrospectively. Forensic and medical documents in the files of a total of 148 sexual assault-abuse cases were evaluated in terms of the parameters in the data analysis form, and those who did not have data in the file content related to the parameters in the form were excluded from the study.

Cases were evaluated in terms of various parameters including gender of the victim, age at the time of the incident, marital status, education status, consent to the sexual act, place of sexual abuse, type of sexual act, anogenital examination findings, whether the assailant ejaculated during the attack, use of lubricants, and /or condom, duration of sexual abuse, psychological examination findings, the relationship between mental examination findings and penetration, the relationship between mental examination findings and the number of acts and penetration, exertion of violence during the act, relationship between mental examination findings and a similar attack history, biological sampling, examination time, sex, age and the number of aggressors, relationship between the aggressor, and the victim, and decision of the court.

Descriptive statistics were presented with frequency, percentage, mean (mean), standard deviation (SD), minimum (min), maximum (max) values. In the comparison of categorical variables; statistical relationships between the data were investigated using the chi-square test, Monte Carlo Fisher Exact test, and Mental Henzen test. Analyzes were made with the SPSS 20.0 package program. P values less than 0.05 were considered statistically significant.

RESULTS

This study included 148 cases: 131 (88.5%) cases were female and 17 (11.5%) were male (Table 1).

Table 1. Characteristics of the victims

	n	%
Gender		
Male	131	88.5
Female	17	11.5
Age		
0-12 years	31	20.9
13-15 years	52	35.2
16-18 years	28	18.9
≥ 19 years	37	25.0
Educational status		
Primary	74	50.0
Lycée	24	16.2
University	5	3.3
Unknown	41	27.7
Kindergarten	2	1.4
Illiterate	2	1.4
Total	**148**	**100**

The mean age was 18.6±11.6 (min:4, max:83). The highest number of cases were in the 13-15 age group with a rate of 35.2% (n=52) (Table 1). All male cases (n:17) were single. While 86.2% (n:113) of female cases were single, married (n=4: 3.1%), or widowed/divorced (n=14: 10.7%), and there was no information about the marital status of the other female cases. Half of the cases (n=74) were primary school students (Table 1). The sexual abuse took place mostly at home (n=82: 55.4%) (Table 2). Sexual abuse most frequently occurred through vaginal penetration (n=72: 48.6%) (Table 2). Of 86 cases who underwent vaginal examinations; 44 (51.1%) had old tears in the hymen, 19 (22.1%) had an intact and elastic hymen, 15 (17.4%) had an intact but not elastic hymen. A fresh tear in the hymen was detected in three (3.5%), caruncula hymenalis in three (3.5%), and an intact hymen with a traumatic lesion on labium majus in one (1.1%) case.

Table 2. Characteristics of the sexual abuse

	n	**%**
Crime scene		
Home	82	55.4
Forestland	21	14.2
Street	14	9.5
Car	12	8.1
Derelict building	4	2.7
Forestland – car	3	2.0
Forestland - home	3	2.0
Others	9	6.0
Type of sexual abuse		
Vaginal penetration	72	48.6
Touching – caressing – kissing	35	23.6
Anal penetration	14	9.5
Vaginal + anal penetration	8	5.4
Anal rubbing	5	3.4
Vaginal rubbing	5	3.4
Vaginal + oral penetration	3	2.0
Vaginal rubbing + anal penetration	1	0.7
Touching + kissing + oral penetration	1	0.7
Penetration attempt	1	0.7
Exhibitionism	1	0.7
No exploits identified*	2	1.4
Victim - defendants relationship		
Stranger	27	18.2
Familiar	121	81.8
Social environment	62	41.9
Darlingi	35	23.7
Relative	13	8.8
Incest	7	4.7
Spouse	4	2.7
Total	**148**	**100**

* Although a lawsuit was filed with the allegation of sexual abuse in two cases, it was determined that there was no evidence of sexual abuse. It was learned that one of these cases resorted to the method of lying in order to reconcile with her lover, the other case was abducted, but rescued by the law enforcement shortly after being abducted, and it was learned that any act of sexual abuse did not occur during this process.

Of 68 cases who underwent anal examinations 53 (77.9%) victims had normal anal examination findings, five (7.3%) had chronic fissures, and four (5.8%) had acute fissures. Ecchymosis, hyperemic erosion-abrasion around the anus, total anal dilatation, acute fissure + sphincter insufficiency, acute fissure + decrease in sphincter tone, venous distension were detected separately in one (1.5%) victim for each lesion.

When the duration of exposure of the victims to sexual abuse was investigated, any relevant information could not be found in one case. Ninety-six (64.8%) cases were exposed to sexual abuse once. While 12 (8.1%) cases were exposed to sexual abuse intermittently for 1-30 days, nine (6.1%) cases for 1-3 months, and 30 (% 20,3) cases for more than 3 months. Mental state examination was performed in 111 (75%) cases,

and no psychopathological findings were found in the mental state examination of 65 (58.5%) cases. The mental examination findings of the victims were given in Table 3.

Table 3. Mental examination finding of the victims

	n	%
Mental examination		
No mental illness	65	58.5
Mental illnesses developed after sexual abuse		
Acute stress disorder (ASD)	10	9.0
Post traumatic stress disorder (PTSD)	10	9.0
Major depression	5	4.5
Depressive disorder	3	27
Acute stress reaction	1	0.9
ASD + Depression	1	0.9
Anxiety + Depression	1	0.9
Moderate mental retardation + ASD	1	0.9
PTSD + Major depression	1	0.9
TSSB + Anksiyete	1	0.9
Mental illnesses found before sexual abuse		
Moderate mental retardation	5	4.5
Mild mental retardation	4	3.7
Severe mental retardation	1	0.9
Demantia	1	0.9
Antisocial personality disorder	1	0.9
Total	**111**	**100**

No statistically significant difference was found between the occurrence of the sexual act once or more than once and the development of a mental disorder after the event (p>0.05) (Table 4).

In 61 (41.2%) cases, at least one or more types of violence were used during the incident. When the types of violence perpetrated during the sexual assault were examined; threats were reported in 28 (25.2%), physical violence in 25 (22.5%), verbal violence in 19 (17.1%), and use of weapons or tools in 16 (11%) cases. No statistically significant difference was found between those who were exposed to any type of violence other than sexual violence during the event and those who did not, in terms of the development of mental symptoms (p>0.05) (Table 4). However, when the types of violence were evaluated separately, it was determined that verbal violence and threats during and after the event did not cause mental disorders (p>0.05), while physical violence was statistically influential in the development of mental disorders after the event (p=0.008) (Table 4).

Table 4. The relationship between total violence, verbal violence, physical violence,sexual activity, similar attack history and post-event mental disorder development.

	Mental Disorder		
	No	**Yes**	**P***
	n(%)	n(%)	
Total violence			
Yes	26(33.8)	18 (53)	0.57
No	51 (66.2)	16 (47)	
Threats			
Yes	16 (20.7)	12 (35.2)	0.105
No	61 (79.3)	22 (64.8)	
Verbal violence			
Yes	11 (14.2)	8 (23.5)	0.233
No	66 (85.8)	26 (76.5)	
Physical violence			
Yes	12 (15.5)	13 (38.2)	0.008
No	65 (84.5)	21 (61.8)	
Sexual activity			
Once	51 (66.2)	23 (67.6)	0.884
More than one	26 (33.8)	11 (32.4)	
Similar attack history			
No	55 (71.4)	28 (82.3)	0.222
Yes	22 (28.6)	6 (17.7)	
Total	**77 (100)**	**34 (100)**	

*Pearson Chi-Square Test

In this study, a total of 30 (20.2%) cases were found to have a similar attack history in the past. Six (21.4%) of the cases with event-related mental illness had a similar attack history before the event. No statistically significant difference was found between the history of a similar attack in the past and the incidence of post-event mental disorder (p>0.05) (Table 4). A statistically significant difference was found between the history of a similar attack and the presence of a traumatic lesion related to the event (p=0.007) (Table 5). In addition, a significant difference was found between marital status and lesions detected on physical examination (p=0.029) (Table 5). It has been determined that the traumatic lesion related to the event is seen at a lower rate in single people than in non-single people.

Table 5. The relationship between similar assault history and marital status and the presence of traumatic findings.

		Traumatic findings		
		No	**Yes**	**p**
		n(%)	n(%)	
Similar attack history				
	Yes	28 (31.1)	1 (4.2)	**0.007***
	No	62 (68.9)	23 (95.8)	
Marital status				
	Single	83 (92.2)	18 (75)	**0.029¹**
	Not single	7 (7.8)	6 (25)	
Total		**90 (100)**	**24 (100)**	

*Pearson Chi-Square Test ¹Fisher's Exact Test

Biological samples were taken in only 23.6% (n:35) of our cases, and 20 (57.1%) of 35 cases were examined in the first seven days after the event while positive results were obtained in eight (40%) cases.Sixteen (10.8%) cases did not undergo physical examination after the event. While 60 (45.5%) out of the remaining 132 cases were examined within the first 7 days, 23 cases (17.4%) within 7-30 days, seven cases (5.3%) within 1-3 months and 42 cases (31.8%) > 3 months after the incident. In all cases, it was determined that the aggressor was a single person. All of the attackers were male and their mean age was 37.8±15.3 (min:13, max:89) years. When the aggressor-victim relationship was classified; it was determined that 121 (81.8%) assailants consisted of people who were recognized by the victim (Table 2).

DISCUSSION

Today, sexual assault has become a widespread and serious social danger. One of the important problems regarding sexual assault, which has become a global problem; assaults can be repetitive, multiple, and exerted together with verbal or physical violence. Although sexual assault is an important social danger for both genders, there is no doubt that women are affected much more frequently in social life. Females are 2-5 times more likely to be exposed to sexual assault than males (5). However; in a long-term study, Mathews et al., found that from 1993 to 2012 in Australia, there was a 2.6-fold increase in the rate of sexual abuse in males and 1.5-fold in females (7). In a recent study of 1614 adolescents in India, it has been reported that 36% of males and 35% of females have been exposed to sexual abuse at some point in their lives (8). In studies conducted in Turkey, it was determined that 82.7% - 96.2% of the victims of sexual abuse were female (9–11). Consistent with the literature, in this study, 88.5% of the victims (n=148) of sexual abuse and assault cases were female and 11% were men.

It has been reported that the age of sexual abuse in girls is higher than that in boys, and the risk of sexual abuse in girls increases with age (12). In this study mean ages of female, and male victims were determined as 119.46±11.82 (min:4, max:83), and 2.76±8.01 (min:5, max:38) years, respectively. In Turkey, the rate of children among all victims of sexual assault varies between 63.3% and 63.8% (10,13). In a study examining the demographic characteristics of children aged < 18 (n=138) years, and under the risk of sexual abuse, it was found that the majority of the victims were girls, and the age distribution peaked at the age of 3 and 15 years (14). In a study conducted on 275 cases of sexual abuse in Konya, it was determined that the highest number of cases were accumulated in the 12-15 age group (45.8%) (15). In this study, consistent with all these data, it was determined that 75% of the victims were < 18 years old, and the highest number of cases was in the 13-15 age group with a rate of 35.2% (n=52).

Yıldırım et al. reported that more half of (53.2%) sexual assault victims were single (16). In two studies conducted in Turkey, it was reported that 89.1% and 90.4% of the victims were single and never married, respectively (17,18). Similarly, in this study, 86.8% (n=112) of the female, while all (n=17) of the male victims were single.

In Turkey, it is known that victims of sexual abuse are mostly in the primary or secondary school age or illiterate (17,19). Yıldırım et al. investigated a total of 109 cases and reported that seven (6.4%) cases were illiterate, 26 cases (23.9%) were primary school, 55 cases (50.5%) were secondary school, and 21 cases (19.3%) were higher education graduates (16). In this study, half of the cases (n=74) were primary school students. In a three–year study conducted in Kahramanmaraş, it was reported that 66.6% of sexual abuse victims were exposed to sexual assault at home (13). In their study involving 324 victims of sexual abuse, Karanfil et al. reported that sexual assault occurred frequently (61.1%) at the home of the victim or the accused (11). In another study conducted in the Konya Province, it was determined that acts of sexual abuse frequently took place in the house environment (44.7%) (15). In this study, sexual abuse was most frequently happened at home (n=82: 55.4%). The reason why sexual assaults often occurred at home may be that the familiar accused was more likely to be alone with the victim at home and more likely to be invisible.

In studies examining the way the sexual act occurred, it was determined that the most common type of sexual abuse reported in girls was vaginal penetration, and in boys anal penetration (19). In a study performed in India involving 40 victims of sexual abuse under the age of 16, vaginal penetration (55%) was reported as the most common type of sexual abuse (20). In a study involving 1076 cases in the age range of 1-85 years; 79% of cases had been exposed to vaginal penetration, 25% to oral penetration, and 17% to anal penetration (21). Perdahli et al. conducted a study on 83 children and adolescents who were victims of sexual abuse, and reported that the most common type of sexual abuse was genital friction without penetration (44.6%) (22). In the study by Dönmez et al. involving a total of 215 children and adolescents, sexual abuse involved touching to genital area in 89.8% (n=193) penetration in 46% (n=100) of the victims, and the most common type of sexual abuse was touching the body of the girls for sexual satisfaction in 42.7%, and anal penetration in boys in 50% of the cases (23). In a recent study involving a total of 482 pediatric cases; it has been stated that the most common type of sexual abuse was vaginal penetration in girls and anal penetration in boys (24). In this study; the most common type of abuse was vaginal penetration.

Heger et al. reported that only 14.6% of girls with acute genital injuries had anatomical changes that left traces (25). In their study involving 1500 children under the age of 17 who underwent anogenital examination, Gallion et al. stated that only 7% of the cases had diagnostic anogenital examination findings (26). In addition; it has been reported that anal lesions heal quickly and usually do not leave any scars (25). It has been claimed that fecal incontinence, anal fissure, anal laceration, total anal dilatation are associated with anal penetration, and total anal dilatation was statistically correlated with the history of anal penetration, especially in girls (27). Demirci et al. reported old and new hymen ruptures, elastic, and inelastic hymen in 36.8%, 5.9%, 12 %, and 48.5% of their sexual abuse, respectively. They also reported normal anal examination findings in 91.3%, acute sodomy findings in 6.1%, and chronic sodomy findings in 2.6% (15). In this study, old tears in the hymen (n=44: 51.1%), an intact elastic hymen (n=19: 22.1%), inelastic intact hymen (n=15: 17.4%), a fresh tear in the hymen (n=3: 3.5%), caruncula hymenalis (n=3:3.5%), intact infantile hymen (n=1: 1.1%) , and intact hymen with a lesion on the labium majus (n=1: 1.1%) were detected in 86 cases who underwent hymen examination. Of 68 cases that underwent anal examination; there were normal anal examination findings in 53 (77.9%), chronic fissures in 5 (7.3%), acute fissures in 4 (5.8%) cases, also, ecchymosis around the anus, hyperemic erosion – abrasion on the periphery of the anus, total anal dilatation, acute fissure + sphincter insufficiency, acute fissure + decrease in sphincter tone and decrease in sphincter tone, venous distension were detected in a one case for each lesion (n=1: 1.5%).

Gençoğlan et al. reported that 12.2% of the cases were exposed intermittently to sexual abuse for 1 year or longer, 8.9% within 1 month - 1 year, and 1.1% within 1 week - 1 month (19). In this study, when the duration of exposure to the sexual act of the victims was examined; there was no information about one case, and while 96 (64.8%) cases were exposed to sexual assault once, 12 (8.1%) cases between 1-30 days, nine (6.1%) cases for 1-3 months, 30 cases (% 20,3) for more than 3 months.

It has been shown that child sexual abuse caused lifetime increase in the risk of anxiety disorder, depression, eating disorder, PTSD and sleep disorders (28). Bhaskar et al. stated that depressive disorders were most prevalently seen in children of sexual abuse (35%) followed by stress-related such as ASD and PTSD (25%), and that children who have been abused more than once are more likely to suffer from a psychiatric illness after sexual abuse (20). According to the results of a study conducted in Turkey; It was reported that at least one psychiatric illness was detected 45.6% (n=41) of the victims of sexual abuse and the most common mental illness was PTSD with a rate of 28.9% (n=26) (19). Dönmez et al. included 215 children and adolescents in their study, and reported that 81.9% of the cases (n=176) had at least one post-abuse mental disorder (PTSD, 33%; ASD, 25.6%; major depressive disorder, 25.1%; conduct disorder, 2.8% (23). Korkmaz et al. reported that 49 (19%) of 258 sexual abuse victims had deteriorated physical or mental health (17). Perdahli et al. reported that victims of sexual abuse under the age of 18 were most frequently diagnosed with anxiety disorders (36.1%) and adjustment disorders (22.9%) (22). In this study, it was determined that 111 (75%) cases were subjected to psychiatric examination, and 34 (30.7%) of them were found to have post-event mental illness. These results suggest the effects of heterogeneity in childhood sexual development. When the psychiatric diseases detected in our cases were analyzed, in accordance with the published data; ASD and PTSD were in the top ranks. There was no statistically significant difference between the findings of the psychological state of the victims in our study and the age groups. No statistically significant difference was found between the occurrence of a sexual act once or multiple times and whether a mental disorder occurred after the event.

It has been reported that victims of sexual abuse are more likely to report the abuse to the police if they develop a physical injury (29). The act of protection is closely related to the physical injury of the victim (16). In particular, this relationship is most evident with physical resistance

(30). Ezechi et al. reported that 31% of sexual abuse victims were exposed to threats and 29.6% to physical violence (31). In a study involving 268 child and adolescent sexual abuse victims, it was found that 28.4% of the cases had general body trauma and 13.1% were threatened with a gun or knife (32). In 61 of our cases (41.2%), at least one or more types of violence was used during the incident. In this study, threats were reported in 28 (25.2%), physical violence in 25 (22.5%), verbal violence in 19 (17.1%), and use of weapons or tools in 16 (11%) cases. In addition, only physical violence was found to be statistically influential in the occurrence of mental disorders after the event.

Many studies have found that sexually abused children are more likely to be sexually abused again later in both adolescence and adulthood. This situation also creates a basis for potential mental disorders to be experienced in the future. In their long-term prospective study involving 93 girls with a confirmed history of child sexual abuse, Barnes et al. reported that 40% of the cases were victims of re-abuse and the mean age of re-abused cases was 13.47 years (33). In Hornor and Fisher's study, which included 198 children, 100 cases were the first victims of sexual abuse and 98 children were victims of sexual abuse before; It was stated that children who were victims of recurrent incidents of sexual abuse were at a younger age, and they were at higher risk of developing mental health problems with developmental delay (34). Magnusson et al. determined that 64.9% of 57 pre-school children who were victims of sexual abuse were exposed to abuse several times (35). Gençoğlan et al. reported that 31.1%.of their pediatric population was exposed to sexual abuse more than once (19). Demirci et al. reported that 157 (57.1%) cases were exposed to sexual abuse once, and 72 (26.2%) cases more than once (15). In this study, it was determined that 30 (20.2%) cases had a similar assault history in the past. Among victims in whom mental symptoms were detected during post-event mental state examination, history of similar assault were elicited in 6 (21.4%) cases. There was no statistically significant difference in the incidence of mental disorders between individuals with a similar attack history and those who were victims of the sexual abuse for the first time. However, a statistically significant difference was found between a similar attack history and the presence of (if any) a traumatic lesion related to the event. It has been thought that this finding may be due to the fact that the victims who are abused for the first time show more resistance to the accused, and accordingly they are exposed to more severe physical violence. In addition, a significant difference was found between marital status and lesions detected on physical examination. It has been determined that the traumatic lesion related to the event is seen at a lower rate in single people than in married people.

Young et al. reported that in only 16 (20%) of 80 sexual abuse cases semen was detected in samples, and all of these semen-positive samples were taken within 24 hours after the incident (36). Schilling et al. reported that 74% of the cases were examined within the first 72 hours after the incident (37). In a study involving 341 sexual abuse cases, it was reported that 43.4% of the cases were examined within the first seven days after the incident (10). It was determined that 45.5% (n:60) of our 132 cases were examined within the first 7 days. Besides biological samples were obtained from only 35 cases (23.6%), and 20 of them (57.1%) were examined within the first seven days after the event, while positive results were obtained in eight (40%) of them. It is seen that more than half of the victims surveyed in our study were sent for examination more than seven days after the incident. In addition, it was thought that sending the victims to the examination too late, was also responsible for the low biological material intake rates.

In studies conducted in Turkey, all sexual abuse and assault suspects were reported to be male (16,17). Similarly, all the assailants in this study were male. Steine et al. found that the majority of perpetrators were biologically related parents (38.4%) or trusted acquaintances (76.1%) (38). Studies conducted in Turkey have indicated that 54.4-94.4% of the defendants are known to the victims (13,19,23). In this study, the aggressor was a person known to the victim in vast majority of cases.

CONCLUSION

Offenses against sexual immunity are a global danger with multifactorial etiology, and increasing worldwide prevalence that concerns not only the individual but also the whole community. In our study, it is seen that sending the victims to the examination too late was effective on the low biological material intake rates. The delay in seeking medical care may be related to the victim's attitude towards hiding the sexual abuse because of the guilt, shame and/or fear experienced after the sexual act. Considering that sexual abuse and assaults are increasing day by day; apart from basic sexual education provided for the children and adolescents at school, education should also be focused on how to protect them against sexual abuse. Family-based assistance and education programs should be expanded throughout the country. Most of the time, the evaluation of cases by non-specialist physicians causes loss of findings and thus evidence. Therefore after the incident, the victim must be examined by a forensic medicine specialist, a psychiatrist, and other specialist physicians depending on the nature of the incident,

and implementation of necessary examinations must be ensured.

The problems of the existing Child Monitoring Centers should be examined in detail and rehabilitated meticulously, then their numbers of these institutions should be increased and they should be established in every city. In the second stage, centers should be established in accordance with international standards, where adult sexual abuse cases can apply after the incident, forensic and medical procedures will be completed in the same building, necessary medical support and treatment will be provided, and should be expanded throughout the country. Determining the risk factors for sexual assault-abuse crimes in our country with larger studies to be carried out throughout the country will be beneficial for the development of sexual assault-abuse prevention strategies at the national level.

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RESEARCH ARTICLE

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The Effect of Periodic Examination Time Interval and Frequency After “Percutaneous Coronary Intervention” on Experiencing Second "Acute Coronary Syndrome"

ABSTRACT

Objective: The aim of this study was to evaluate the effect of follow-ups of patients who underwent percutaneous coronary intervention (PCI) at short (<6 months) and long-term intervals and media on their experiencing attacks of acute coronary syndrome (ACS).

Methods: The data of 281 patients who underwent twice PCI in our clinic were retrospectively analyzed. The patients were divided into two groups as those who came to the controls regularly at intervals of ≤ 6 months (Group 1, n: 157) and those who came irregularly or at intervals of more than 6 months (Group 2, n: 124). We investigated whether regular periodic controls have any positive effect on adequate statin use, experiencing acute coronary syndrome episodes and cardiac mortality.

Results: In Group 2; frequency of ACS [87.8% versus 20.6%, p<0.001], insufficient use of statins [86.4% versus 16.7% p <0.001], and withdrawal of statins by media influence [64.0% versus 5.1% p <0.001] was higher than Group 1.

Conclusions: Looking at the results of the study; it can be said that regular follow-up of patients with a cardiac event at 6-month intervals reduces the rate of acute coronary syndrome experience and treatment compliance is better in these people.

Keywords: Acute Coronary Syndrome, Angioplasty, Follow-Up Studies, Therapeutics Compliance.

“Perkütan Koroner Girişim” Sonrası Periyodik Muayene Zaman Aralığı ve Sıklığının İkinci "Akut Koroner Sendrom" Yaşanmasına Etkisi

ÖZET

Amaç: Bu çalışmayla perkütan koroner(PKG) girişim geçiren hastaların 6 aydan kısa ve uzun sürelerle kontrol edilmelerinin ve medyanın akut koroner sendrom(AKS) yaşamalarına etkisi araştırılmıştır.

Gereç ve Yöntem: Kliniğimizde iki kez PKG geçirmiş 281 hastanın bilgileri retrospektif olarak incelenmiştir. Bu hastalar 6 ay ve daha kısa süreli düzenli takibe gelenler (Grup 1, n: 157) ve 6 aydan uzun sürelerle veya düzensiz takibe gelenler (Grup2, n: 124) ve olarak iki gruba ayrılmışlardır. Düzenli takiplerin yeterli statin kullanımında, akut koroner sendrom geçirmede ve kardiyak sebeple ölüm üzerinde etkili olup olmadığı araştırılmıştır.

Bulgular: AKS sıklığı (87.8 e karşı 20.6% <0.001), yetersiz statin kullanım oranı[86.4 e karşı 16.7%, p<0.001], medyanın etkisiyle (%64.0 e karşı %5.1, p<0.001) statin kullanımını bırakanların oranı, Grup 2 de, Grup 1 den yüksek bulunmuştur.

Sonuç: Çalışmanın sonuçlarına bakılınca; kardiyak olay yaşayan hastaların 6 ay aralarla düzenli takibe gelmelerinin, akut koroner sendrom yaşama oranlarını azalttığı ve tedavi uyumunun bu kişilerde daha iyi olduğu söylenebilir.

Anahtar Kelimeler: Primer Perkütan Girişim, Akut Koroner Sendrom, Düzenli Klinik Takip, Tedavi Uyumu.

INTRODUCTION

Acute coronary syndrome is an important cause of morbidity and mortality in the community. Patients who undergo primary PCI are more likely to have a new ACS compared to other members of the population (1, 2). Despite a successful intervention, patients outcomes may not be good enough unless regular follow-up and treatment is provided. The first month after discharge is the period when the morbidity and mortality rates are the highest. Therefore, it is very important for the patients to get in close contact with their physicians in the first month, and to be followed closely by their physicians in the following months. Even in patients who have not undergone percutaneous intervention, strict medical treatment and aggressive LDL-lowering therapy reduce the patient's chance of experiencing acute coronary syndrome and improve quality of life (3-8). Adequate medication reduces the likelihood of patients experiencing a second event. Regular check-ups are of great importance to ensure this. In studies investigating the efficacy of the treatment, optimum results can be obtained since patients are followed regularly. In reality, regular follow-ups are often not provided. It is very important to inform patients who are followed up irregularly, do not want to use medication, or receive insufficient statin therapy. Regular follow-up of patients can help detect new events early and thus increase the survival rates of patients (9-13). Moreover, lowering LDL below 55 mg / dl decreases the possibility of ACS in patients with coronary artery disease (14).

In the current study, we aimed to investigate how regular follow-ups at 6-month intervals affect drug use, the possibility of experiencing a second ACS attack, and whether it has any effect on cardiac mortality.

MATERIAL AND METHODS

Patient Selection and Study Design: A total of 3285 patients who underwent PCI between 2011 and 2017 were scanned to determine the frequency of periodic examinations of patients who underwent two or more PCIs. A total of 345 patients who underwent PCI for the second time were identified. The data of patients who underwent second PCI were obtained by medical hospital computer systems. In consultation with the patients and their relatives, it was determined which factors affected the patient's compliance with treatment, whether they were treated in another institution or whether they participated in regular follow-ups in another institution. Two hundred and eighty one patients who remained after the exclusion criteria were applied were included in the study. Patients eligible for the study were divided into two groups as Group 1 (n: 157) who participated in control visits regular or less than 6 months and Group 2 (n: 124) who participated in control visits irregular or later than 6 months (Figure 1). Age, gender, mean follow-up period, diabetes, hypertension, hyperlipidemia, history of CABG, presence of peripheral arterial disease, blood creatine levels, body mass index (BMI), presence of prevalent coronary artery disease in the family, smoking status of the patient, use of beta-blockers, antiplatelet medicines, ACE inhibitors, ARB and vasodilator medicine were recorded.

Exclusion Criteria of the Study: Patients who were followed for less than a year were excluded from the study, as shorter follow-up time may impair statistical significance in comparisons. Furthermore, the disabled or too old patients, patients whose attendance to control visits was hardly possible, and those who would not be able to come for control visits for various reasons were excluded from the study. Patients who were not residing in city of the study and who could not attend the control visits were not included in the study. Moreover, patients with end-stage chronic diseases and cancer with short life expectancy were also excluded from the study. This study complied with the Declaration of Helsinki, and it was approved by the independent medical ethics committee of Sakarya University Education and Research Hospital.

Study Endpoints: The primary end-point of the study was the presence of acute coronary syndrome in the second procedure. Cases with acute myocardial infarction with or without ST elevation were recorded. The median follow-up period of the patients included in the study was 5 years. For this reason, 5-year cardiac mortality rates were recorded based on the median follow-up period and determined as the primary endpoint in the comparison. Inability to reduce LDL levels down to 70 mg/dL and / or use of $\leq$ 10 mg rosuvastatin, $\leq$ 20 mg atorvastatin, $\leq$ 40 mg simvastatin and pravastatin were defined as low dose or less effective statin therapy (15).

In clinical follow-ups, patients were asked whether they discontinued the medication, and why, how they were affected by the media, whether the medicine had side effects, or the medicine was discontinued or its dose was reduced due to prescription problems. Questions and answers were standardized and recorded for comparison.

The fact that medicines cannot be prescribed regularly is an important problem in our country. The patients are complaining that they cannot take their medications regularly because they are not prescribed regularly and physicians cannot prescribe medication due to certain stipulations imposed by SGK (Social Security System = the health insurance institution of Turkish government).

Statistical Method: Continuous variables were compared with “independent sample t test within 95% confidence interval. Mean values were

given together with ± standard deviations and intragroup percentages. Sig.2: P values were measured Levene's equality of variances test, t-test, and equality of means. The difference was considered significant if both p values were less than 0.05. Nominal data were analyzed by Pearson's chi square "and cross- table" test. P values less than 0.05 were considered significant.

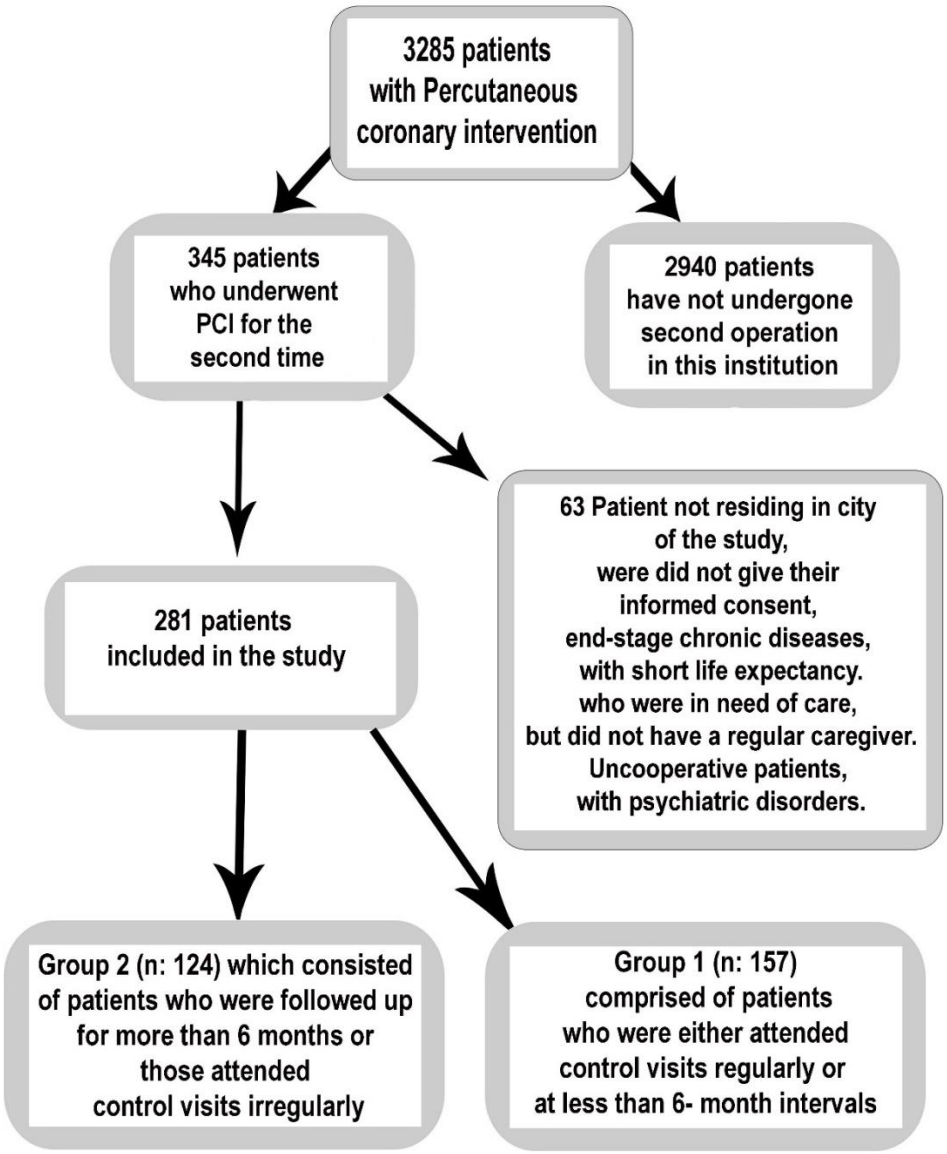

Figure 1. Algorithm of the study

RESULTS

Both groups were comparable in terms of age, female sex, education level, smoking status, diabetes, hypertension, and hyperlipidemia, history of CABG, body mass index (BMI), ejection fraction, peripheral vascular diseases, and blood creatine levels. In Group 1(n: 157), the mean follow-up period was shorter when compared with Group 2(n:124) (4.53 ± 1.24 vs 4.99 ± 1.08 / year p = 0.001).

Regarding the second procedure, both groups were comparable in proportion of patients in terms of Killip 3,4 class [12.3% (n: 7/57) vs 11.3% (n: 11/96) p = 0.861], in whom the same vessel was intervened in the second procedure [35.2% (n: 44/124) vs 31.2% (n: 49/157) p = 0.479], those discontinuing the statin treatment due to its side effects [1.6% (n: 2/124) vs 1.9% (n.3 / 157) P = 0.844], patients whose target lesion was in-stent restenosis in the second procedure, [2.2% (n: 4/124) vs 1.9% (n: 3/157) P = 0.483], ACE inhibitor or ARB users . [82.4% (103/124) vs 87.8% (n: 138/157) p = 0.193], betablocker users [55.2% (n: 69/124) vs 58.0% (n: 91/157) p = 0.642], nonusers of vasodilator medicines [72.0% (n: 90/124) vs 75.2% (n: 118/157) p = 0.549]. Regarding second procedures both groups were compared in terms of the presence of primary PCI [87.8% (n: 108/124), vs 20.6% (n: 32/155) p <0.001], cardiac mortality rate [9.6% (n: 12/124) vs 1.9% (n: 3/157) p = 0.004], ineffective statin

treatment [86.4% (n: 107/124) vs 16.3% (n: 20/157) p <0.001] , stopped using antiplatelet medicines [15.2% (n: 19/124), vs 1.9% (n: 3/157) p <0.001], those quitting statin treatment under the influence of adverse antimedicine propaganda in the media [%64.0 (n:80/124) vs. %5.1 (n:8/157) p<0.001] , due to prescription problems or usage of ineffective doses of statin ([20.0% (N: 25/124 vs. 5.7% (N: 9/157) p <0.001]). However patients with primary education only [64.8% (n: 81/124) vs. 51.0% (n: 80/157) p = 0.020] and/or higher LDL levels [122.53 ± 36.27 mg/dL vs. 74.62 ± 26.13 mg/dL p <0.001] were more frequently detected in Group 2 when compared with Group 1 (Table 1 -2).

Table 1. Baseline demographics and clinical presentations of groups.

	Patients with irregular follow-up (Group 2) N:124	**Patients with Regular follow-up (Group 1) N:157**	**P**
Age (years)	65.79±9.92	65.71±10.59	0,525
Female Gender	30.1% (n:37/124)	31.2 % (n:49/157)	0.839
Mean follow-up period (years)	4,53±1.24	4.99±1.08	**0.001**
Functional class (Killip 3-4)	12.3% (n:7/57)	11.3% (n:11/96)	0,861
High Education Level	35.2%(n:44/124)	49.0%(n:77/157)	**0.020**
Smoking Status	32.8% (n:40/122)	21.0%(33/157)	**0.029**
Diabetes Mellitus	61%(n:66/104)	49.5%(n:55/111)	0.072
Hypertension	84%(n:84/100)	86.6%(n:97/112)	0.592
Hyperlipidemia	86.6%(n:97/112)	84.8%(n:112/132)	0.696
Previous CABGa	15.3%(n:19/122)	16.6%(n:26/157)	0.779
Family history of CAD b	78.6%(n:92/117)	87.8(n:122/139)	**0.049**
BMI kg/m2	29.63±2.82	29.01±3.71	**0.045**
EF d(%)	46.56±8.92	50.74±8.55	**0.004**
Peripheric Vascular Disease	50.0%(n:62/124)	45.8%(n:84/155)	0.486
Ineffective Statin use	86.4%(n:107/124)	16.3%(n:20/157)	**<0.001**
LDL Level (mg/dl)	122.53±36.27	74.62±26.13	**<0.001**
Beta Blocker Use	55.2%(n:69/124)	58.0%(n:91/157)	0.642
Nonusers of antiplatelet medicines	15.2%(n:19/124)	1.9%(n:3/157)	**<0.001**
ACEf inhibitor or ARBg use	82.4%(103/124)	87.9%(n:138/157)	0.193
Nonusers of vasodilator medicines	72.0%(n:90/124)	75.2%(n:118/157)	0.549
Creatinine level (mg/dl)	0.98±0.24	1.11±0.57	**0.012**

a Coronary artery bypass graft, b Coronary artery disease, c Body mass index, d Ejection fraction, e Percutaneous coronary intervention, f Angiotensin converting enzyme, g Angiotensin receptor blockers.

Table 2. Clinical outcomes and procedural characteristics of groups

	Patients with irregular follow-up (Group 2) N:124	**Patients with regular follow-up (Group 1) N:157**	**P**
Second procedure PCI	84.6%(n:104/124)	20.6%(n:32/155)	**<0.001**
In-stent Restenosis	2.8%(n:8/124)	1.4%(n:4/157)	0.094
Second intervention to the same vessel	36.2%(n:45/124)	31.3%(n:49/157)	0.376
Annual (%)cardiac mortality rate	9.6%(n:12/124)	4.5%(n:7/157)	**0.106**
Target vessel in the second procedure			
LAD or related graft	26.6%(n:33/124)	34.4%(n:54/157)	0.194
Cx or related graft	39.5%(n:49/124)	33.8%(n:53/157)	0.321
RCA or related graft	33.9%(n:42/124)	31.8%(n:50/157)	0.408

PCI, Percutaneous coronary intervention.

DISCUSSION

PCI patients who do not come to the follow-up visits periodically and at frequent intervals may be affected adversely by some publications in the media, and some negative situations in their social environment consequently they forget important information about their illnesses and medications over time, eventually they stop their medicine treatment, or reduce their medicine doses. In regular follow-ups, patient information and patient education can be said to have a positive effect on patients' clinical processes and health status. How important is the follow-up period on patients? How

often should follow-ups in the outpatient clinics be performed? Clinical experience suggests that patients who are followed up at intervals of more than 6 months forgot what they have learnt about their treatment (2, 10,16).

Patients who attended follow- up visits at long intervals forget important information. Besides, they are under the influence of anti-medicine publications in the media. Unfortunately, the negative impact of the media in our country causes patients to have a negative opinion, especially about statin use. Patients affected by the media think that statin is harmful and should not be used. So they stop using their medications. This neglect causes further progression of the disease in the coronary arteries, which are already atherosclerotic, and increases the rate of patients having heart attacks (5,6,16).

In a study investigating the effect of media on statin use in the UK in 2016, it was found that - as in our country- statin users, though not statistically significant number of patients, quitted statin use under the negative influence of media (17). In a very valuable study that investigated the effect of media on statin use in our country. It was found that at least 50% of patients who had to use statins had stopped using them within 5 years, and at least 60% of those who had not stopped using them were receiving insufficient doses of the medicine (17).

When we analyzed the results of the studies and our study, it is understood that 50% of the patients in the risk group either stopped statin treatment or reduced the dose of the medicine to an ineffective level due to anti-medicine propaganda in the media. In addition, 93% of the patients who refused to use statins despite contrary recommendations they cite anti-statin news in the media as the reason for their refusal (17,18).

Most of the patients who are against the use of medication, think that they protect themselves against risks by natural therapy. Unfortunately, the level of education does not have a positive effect on this issue. For example, when we investigated whether the level of education obviates negative media impact urging patients to quit their medications among all participants, the rate of cessation of therapy was not different between participants with higher and lower education levels. Fortunately, this withdrawal rate was not statistically significant lower at higher education level when compared with those with lower education level. This is a bit pleasing.

The proportion of highly educated persons in the regular follow-up group is significantly higher than that in the irregular follow-up group. [49.0% (n: 77/157) vs 35.2% (n: 44/124) p = 0.020]. In other words, people with a higher education level paid more attention to their health and attend follow-up visits more regularly (Table 3).

Table 3. The association between statin use, education level, regular follow-up

	Subgroup of <6-month /Irregular Follow-ups		
	Poorly educated	**Well Educated**	**P**
Quitters of medicine therapy	6.2%(n:5/80)	3.9%(n:3/77)	0.303
	Subgroup of > 6- month /Irregular Follow-up		
	Poorly educated	**Well Educated**	**P**
Quitters of medicine therapy	58.5%(n:48/82)	68.2%(30/44)	0.288
	All participants		
	Poorly educated	**Well Educated**	**P**
Quitters of medicine therapy	32.9%(n:53/160)	27.3%(n:33/120)	0.308
	Subgroup of well educated		**P**
Quitters of medicine therapy	< 6-month follow-up	> 6- month follow-up	
Quitters of medicine therapy	68.2%(n:30/44)	3.9%(n:3/77)	<0.001
	Subgroup of poorly educated		
Quitters of medicine therapy	< 6-month follow-up	> 6- month follow-up	P
Quitters of medicine therapy	59.3% (n:48/81)	6.2%(n:5/80)	<0.001

In addition, it was seen that the level of education is in line with short follow-up intervals and more regular follow-up visits. However, being educated cannot protect the person from the negative effects of the environment unless he / she attends regular follow-up visits (17).

This study may be expected to make a complementary contribution to the studies relating to media impact on medicine use and primary and secondary prevention studies. Majority (86.4%) of the patients in the risk group who had undergone percutaneous intervention did not use statin at the dose they should use and therefore they experienced episodes of acute coronary syndrome at significantly higher rates [87.8% (n: 108/124) vs 20.6% (n: 32/155) p <0.001]. They were also appear to be at a greater risk of cardiac mortality when compared with those regularly using adequate doses of statins. [9.6% (n: 12/124) vs. 1.9% (n: 3/157) p = 0.004].

Although the effectiveness of dual antiplatelet therapy and statin therapy in primary and secondary prevention of coronary artery diseases is clearly evident, especially in the media and on the Internet, publications are based on personal observations and preferences, which adversely affect the mass of patients. There is a bias against statin and antiplatelet therapy in patients who follow these publications, unfortunately, patients with this bias are disrupting their treatment (17, 18, 19, 20).

The results of this study also demonstrate the importance of calling the patients at short intervals for regular follow-ups, communicating with the patient and their relatives by face-to-face interviews during patient visits and telling the importance of using the medicine over and over again.

In addition, in clinical follow-ups, it is important to explain the mechanism of acute coronary syndrome onsets and in which situations patients should go to the emergency department or cardiologist. Also the benefits of medicines, especially the purpose of statin therapy should be expounded.

Based on the results of the research; mutual rapport between the doctor and the patient increases both the rate of early recognition of the disease and also the rate of maintenance statin therapy at an effective dose. For example; statin dose was not reduced in patients who had been followed up regularly for less than 6 months. However, it was found that patients who were followed up irregularly and at long intervals stopped taking regular and adequate doses of statin.

CONCLUSION

Anti-medicine, particularly anti-statin propaganda, through visual and written media prevails in our country. This propaganda adversely affects medicine use and increases the rate of experiencing acute coronary syndrome by the patients. From this point of view, the importance of regular follow-up and shorter intervals of less than 6 months is evident in order to neutralize the negative information and negative effects imposed on the patients. It is very important to inform the patient and their relatives about the signs, symptoms, and medications to be used at each visit, as if they are presenting to the clinic for the first time.

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RESEARCH ARTICLE

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Turkish Validity and Reliability of the Satisfaction with Simulation Experience Scale

ABSTRACT

Objective: Research on simulation-based experience focuses primarily on the student's level of knowledge, skills, self-confidence, and satisfaction. There is only one scale in Turkish that can be used to measure satisfaction with the simulation experience. The aim of this study was to establish the validity and reliability of the Turkish version of the Satisfaction with Simulation Experience Scale (SSES).

Methods: The study sample consisted of 130 nursing students from two universities. Data were collected using a student information form, the Turkish version of the Satisfaction with Simulation Experience Scale (SSES-TR) and the Scale of Student Satisfaction and Confidence in Learning (SSSCL). The original SSES was translated into Turkish. Thirteen academics, who were experts in nursing and simulation, were consulted for content validity. Expert feedback was collected in a form to determine the content validity ratio using Lawshe's technique. The Turkish adaptation of the SSES was performed by four linguists to ensure linguistic validity. The correlation between the SSES-TR and SSSCL was determined using concurrent validity and Pearson's Correlation. Internal consistency tests were used to test reliability. The SSES-TR was administered to 35 students as a test-retest with an interval of two weeks to determine its consistency across time. Construct validity was evaluated by confirmatory factor analysis (CFA).

Results: The scale had a content validity index (CVI) of 0.86. The SSES-TR had a Cronbach's alpha (α) of 0.928. The correlation between SSES-TR items and total and subscale scores ranged from 0.492 to 0.749. Test-retest reliability coefficients showed that the SSES-TR total score and subscale scores were compatible. The fit statistics of the 3-factor scale structure according to CFA are at the level of "acceptable fit" according to RMSEA (0.095) and SRMR (0.090).

Conclusions: The SSES-TR is a reliable and valid measure that can be used to assess nursing students' satisfaction with simulation-based experience.

Keywords: Simulation, Experience, Satisfaction, Nursing Students, Validity And Reliability.

Simülasyon Deneyimi Memnuniyet Ölçeğinin Türkçe Geçerlik Güvenirliği

ÖZET

Amaç: Simülasyona dayalı eğitimle ilgili çalışmaların çoğu öğrencilerin bilgi ve beceri edinme, özgüven ve memnuniyet ölçüm sonuçlarına odaklanmaktadır. Simülasyon deneyiminde memnuniyeti ölçen sadece bir Türkçe ölçek vardır. Bu çalışmanın amacı "Simulasyon Deneyimi Memnuniyet Ölçeği'nin" Türkçe geçerlik güvenirliğini yapmaktır.

Gereç ve Yöntem: Çalışmanın örneklemini iki farklı üniversitenin Hemşirelik bölümünde öğrenim gören 130 öğrenci oluşturmaktadır. Veriler Öğrenci Tanıtım Formu, Simulasyon Deneyimi Memnuniyet Ölçeği (SDMÖ), Öğrenmede Öğrenci Memnuniyeti ve Özgüven Ölçeği (ÖÖMÖÖ) kullanılarak toplanmıştır. Türkçe çevirisi yapılan ölçek kapsam geçerliği için hemşirelik alanında uzman, simülasyon uygulamaları yapan 13 akademisyenin görüşüne sunuldu. Uzmanların görüşleri Lawshe Tekniği kullanılarak tek bir formda birleştirilerek kapsam geçerlilik oranı belirlendi. SDMÖ'nin dil geçerliğini sağlamak amacıyla Türkçe'ye uyarlama çalışmaları dört dil uzmanı tarafından gerçekleştirildi. ÖÖMÖÖ ile SDMÖ arasındaki ilişki eş zaman geçerliliği yöntemi uygulanarak Pearson Korelasyonu ile değerlendirildi. Ölçeğin güvenirliği iç tutarlılık testleri ile değerlendirildi. Ölçeğin zaman göre değişmezliğini incelemek için 35 öğrenciye 2 hafta ara ile SDMÖ ölçeği tekrar uygulandı. Yapı geçerliliği, doğrulayıcı faktör analizi (DFA) ile değerlendirildi.

Bulgular: SDMÖ kapsam geçerlilik indeksi (CVI) 0.86'dır. Ölçeğin Cronbach Alfa katsayısı 0.928 olarak elde edildi. SDMÖ maddeleri ile ölçek toplam puan ve ilgili alt boyut puanı arasındaki korelasyon katsayıları 0.492 ile 0.749 arasında değişmektedir. Ölçeğin test-tekrar test güvenirliği incelendiğinde, ÖÖMÖÖ toplam puanı ve alt boyutları için puanların uyumlu olduğu görülmüştür. DFA'ya göre 3 faktörlü ölçek yapısının uyum istatistikleri, RMSEA (0,095) ve SRMR'ye (0.090) göre "kabul edilebilir uyum" düzeyindedir.

Sonuç: SDMÖ hemşirelik öğrencilerinin simülasyon temelli deneyimden memnuniyetlerini değerlendirmek için kullanılabilecek güvenilir ve geçerli bir ölçüm aracıdır.

Anahtar Kelimeler: Simülasyon, Deneyim, Memnuniyet, Hemşirelik Öğrencileri, Geçerlik ve Güvenirlik.

INTRODUCTION

Simulation is an active learning method widely used in nursing education (1). Simulation-based experience (SBE) has recently become popular among nursing educators due to the low number of academics, increasing number of students, patient safety, and malpractice cases (2,3). SBE is conducted in risk-free learning environments where students are allowed to make mistakes and learn from them (4). The debriefing session is a critical stage of SBE (5,6) because it facilitates learning by helping students understand the simulation experience (7).

Simulation-based experience increases nursing students' knowledge, self-confidence, and satisfaction. Inadequate preclinical readiness and low self-confidence in clinical settings cause stress among nursing students and negatively affect their self-confidence and satisfaction. Research, however, shows that simulation-based experience in nursing education improves student confidence and satisfaction (1,8).

Studies on simulation-based experience focus primarily on the student's level of knowledge, skills, self-confidence, and satisfaction (8, 9, 10), but there are only a handful of scales that measure these characteristics. Only one Turkish scale is available for measuring self-confidence and satisfaction (11). The Satisfaction with Simulation Experience Scale (SSES) focuses mostly on debriefing sessions and clinical reasoning and learning. It differs from other scales, because it has items on the debriefing session. Scale diversity allows us to see how useful simulation experiences are for students, which can be used as a guide for both students and educators. The aim of this methodological study was, therefore, to establish a Turkish version of the Satisfaction with Simulation Experience Scale (SSES-TR).

MATERIAL AND METHODS

Population and Sample: The study population consisted of all nursing students (n = 208) from the faculties of health sciences at two different universities in Ankara and Istanbul. A total of 133 students agreed to participate in the study. Three students were excluded because they were unable to complete the research process. Therefore, the final study sample consisted of 130 students.

Data Collection Tools: The student information consisted of items on gender, age, grade level, etc.

The Satisfaction with Simulation Experience Scale (SSES) was developed by Levett-Jones et al. (12). It consists of 18 items scored on a 5-point Likert-type scale (1= Strongly Disagree; 5= Strongly Agree), and three subscales: (1) debrief and reflection (nine items; $\alpha = 0.94$), clinical reasoning (five items; $\alpha = 0.86$), and clinical learning (four items; $\alpha = 0.85$) (12). Higher scores indicate higher satisfaction with simulation experience.

The Scale of Student Satisfaction and Confidence in Learning (SSSCL) was used to determine internal consistency. The Turkish validity and reliability of the scale were established by Unver et al. (2017) (11). The scale consists of 12 items scored on a 5-point Likert-type scale (1= Strongly Disagree; 5= Strongly Agree) and two subscales; satisfaction with learning (five items) and self confidence in learning (seven items). There are no reverse-scored items. The scale total score is the sum of the total subscale scores divided by the number of items. Higher scores indicate higher satisfaction and self-confidence. The SSSCL has a Cronbach's alpha of 0.95 while the subscales have a Cronbach's alpha of 0.91.

Procedure: Written permission was obtained from Tracy Levett-Jones to establish the Turkish validity and reliability of the SSES.

Translation of SSES Items into Turkish/Linguistic Validity: The Turkish adaptation of the SSES was performed by four linguists to ensure linguistic validity. Two independent translators translated the original SSES into Turkish. The Turkish version was back translated into English by two independent translators and compared to the original scale. The SSES-TR was finalized based on the feedback of a Turkish linguist who reviewed the English and Turkish meanings of the scale items.

Content Validity: Content validity refers to the extent to which a measure is representative of all components of the construct it is designed to assess (13). The content validity ratio (CVR) was first developed by Lawshe (1975), whose technique suggests that a panel from 3 to 20 experts be consulted to establish content validity (14,15). In this study, 13 academics, who were experts in nursing and simulation applications, were consulted to establish the content validity of the SSES-TR. They used Lawshe's CVR to assess the items for relevancy and clarity on a scale of 1 to 3 (1 = Appropriate, 2 = Revise, 3 = Remove) and provided feedback. The content validity ratio was calculated, and the SSES-TR was finalized based on experts' assessments (13, 16).

Pilot Test: A pilot test was conducted with 20 students to evaluate the intelligibility of the SSES-TR, which was then finalized based on their feedback.

Criterian Validity: Criterion validity, also known as predictive validity, refers to the extent to which a measure agrees with a firmly established and widely accepted external criterion of the phenomenon being measured. The correlation between the SSES-TR and SSSCL was determined using concurrent validity and the Spearman correlation (13,16). Thirty-five students were

recruited to establish the predictive validity of the SSES-TR.

Reliability: Internal consistency tests were used for scale reliability. Internal consistency is a method of reliability used to determine how correlated items proposed to measure a certain construct are with each other (17). The Cronbach's alpha reliability item total score correlation was evaluated (19).

Test-Retest Reliability: A measure is expected to yield consistent results over time. Test-retest reliability is commonly used to assess the consistency of a measure from one time to another. In this study, thirty-five students were administered the SSES-TR as test-retest with an interval of two weeks to determine its consistency across time.

Ethical Considerations: The study was approved by the Ethical Council for Clinical Research of Ankara Yıldırım Beyazıt University (Protocol No: 2018-61). Written informed consent was obtained from participants prior to participation.

Statistical Analysis: Data were analyzed using the Statistical Package for the Social Sciences (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) at a significance level of 0.05. Age data were tested for normality using the Shapiro-Wilk test and normality plots. Median (min-max) scores were presented for age. Mean ± standard deviation (Mean±SD) were calculated for the items, and for the total and subscale scores. Categorical variables were presented as n (%). A confirmatory factor analysis (CFA) and bootstrapping were performed using R language (v.3.5.1) and the "lavaan" package on RStudio Software (v.1.2.1335). A path diagram was drawn using the "semPlot" package.

Construct Validity: A confirmatory factor analysis (CFA) with a diagonally weighted least square (DWLS) estimator was performed to determine the construct validity of the SSES-TR. Standardized factor loadings (SFL) greater than 0.30 were presented. The Root Mean Square Error of Approximation (RMSEA), Normed Fit Index (NFI) Comparative Fit Index (CFI), Incremental Fit Index (IFI),Tucker-Lewis Index (TFI), ratio of $\chi 2$ to degree of freedom (df), and Standardized Root Mean Square Residual (SRMR) were used to assess model fit (18). $\chi 2$ was taken into consideration together with other fit indices because it is sensitive to large sample sizes and strong intra-item correlations. The criteria for good (or acceptable, at least) fit were as follows: CFI≥0.95, TLI≥0.95, RMSEA<0.06 or <0.08 at most, SRMR<0.08, and $\chi 2$/df<3 (20,21,22). The consistency of the fit indices was estimated using nonparametric bootstrapping with 1000 iterations. The bootstrap results with 95% confidence interval (CI) were presented.

Criterion Validity: Criterion validity was determined using Spearman's rank correlation coefficient for the SSES-TR and SCLS scores.

Reliability: Internal consistency was assessed using Cronbach's alpha coefficient for both the total scale and subscales. Test-retest reliability was investigated using intraclass correlation coefficient (ICC) of a two-way mixed ANOVA design for absolute agreement and single measure.

RESULTS

The majority of participants (84.6%) were women. The median age of participants was 20 years (min-max:18-22). The SSES-TR had high item, subscale and total scores (Table 1).

Table 1. Descriptive Statistics of SSES-TR Items, and Total and Subscale Scores

Items	Mean±SD	Min-Max
Item 1	4.431±0.715	1-5
Item 2	4.485±0.707	1-5
Item 3	4.308±0.955	1-5
Item 4	4.423±0.815	1-5
Item 5	4.415±0.765	1-5
Item 6	4.469±0.728	2-5
Item 7	4.469±0.637	2-5
Item 8	4.500±0.718	1-5
Item 9	4.292±0.849	1-5
Item 10	4.446±0.648	2-5
Item 11	4.377±0.662	2-5
Item 12	4.223±0.760	2-5
Item 13	4.038±0.875	2-5
Item 14	4.500±0.685	2-5
Item 15	4.292±0.772	2-5
Item 16	4.454±0.648	2-5
Item 17	4.446±0.683	1-5
Item 18	4.638±0.543	2-5
SSES-TR total score	4.400±0.494	1.83-5
Debrief and reflection	4.421±0.574	1.33-5
Clinical reasoning	4.317±0.530	2-5
Clinical learning	4.458±0.531	2-5

Content Validity: The SSES-TR items had a CVR of 0.69 to 1.00 while the scale had a content validity index (CVI) of 0.86.

Construct Validity: Table 2 shows the fit statistics of the CFA 3-factor structure and their 95% bootstrap confidence interval, suggesting an "acceptable fit" according to the RMSEA, SRMR and $\chi 2$ / df criteria, and a "good fit" according to the other criteria.

The estimates for covariance parameters between item factor loadings and factors showed that the standard factor loadings ranged from 0.629 to 0.897 while the correlations between the subscales ranged from 0.743 to 0.915 (Figure 1). ($p<0.001$)

The chi-square statistics and p-value for three-factor CFA model were 285,7852 and $p<0.001$ respectively ($\chi 2=285,7852$, $p<0.001$, Table 3). All coefficients were significant (Figure 1) ($p<0.001$, Table 3).

Table 2. CFA Construct Validity Results for SSES-TR

Fit Measures	Good Fit	Acceptable Fit	Model Results (95% CI of Bootstrap)	Fit Status
RMSEA	0 < RMSEA < 0.05	0.05 ≤ RMSEA ≤ 0.10	0,095 (0.076-0.123)	Acceptable
NFI	0.95 ≤ NFI ≤ 1	0.90 ≤ NFI < 0.95	0.973 (0.954-0.988)	Good fit
CFI	0.97 ≤ CFI ≤ 1	0.95 ≤ CFI < 0.97	0.985 (0.965-0.994)	Good fit
IFI	0.97 ≤ IFI ≤ 1	0.95 ≤ IFI < 0.97	0.986 (0.965-0.994)	Good fit
TLI	0.96 ≤ TLI ≤ 1	0.85 ≤ TLI < 0.96	0.983 (0.960-0.993)	Good fit
SRMR	0 ≤ SRMR ≤ 0.06	0.06< SRMR ≤ 0.10	0.090 (0.088-0.161)	Acceptable
χ^2/df	0 ≤ χ^2/df ≤ 2	2 < χ^2/df ≤ 3	2.165 (1.992-4.342)	Acceptable

RMSEA: Root Mean Square Error of Approximation, NFI: Normed fit index , CFI: Comparative Fit Index, IFI: Incremental fit index , TLI: Tucker-Lewis Index, SRMR: Standardized Root Mean Square Residual, df: Degree of freedom

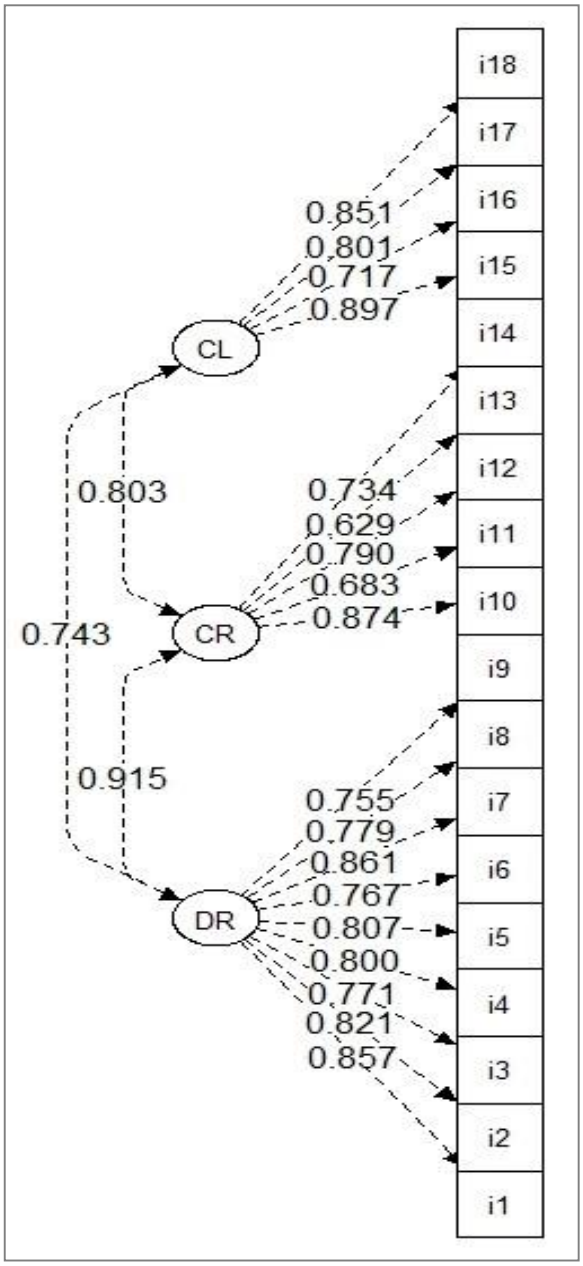

Figure 1. The path diagram of CFA

Table 3. Parameter estimates of CFA model

Path Coefficient of	Standardized Estimate	Standard Error	Z-statistics	p-value
Item 1	0.857	0.039	21.915	<0.001
Item 2	0.821	0.034	24.104	<0.001
Item 3	0.771	0.043	18.080	<0.001
Item 4	0.800	0.039	20.768	<0.001
Item 5	0.807	0.039	20.662	<0.001
Item 6	0.767	0.052	14.610	<0.001
Item 7	0.861	0.034	25.022	<0.001
Item 8	0.779	0.039	19.953	<0.001
Item 9	0.755	0.040	18.960	<0.001
Item 10	0.874	0.038	22.715	<0.001
Item 11	0.683	0.044	15.466	<0.001
Item 12	0.790	0.039	20.051	<0.001
Item 13	0.629	0.057	11.022	<0.001
Item 14	0.734	0.061	12.020	<0.001
Item 15	0.897	0.041	22.118	<0.001
Item 16	0.717	0.053	13.532	<0.001
Item 17	0.801	0.048	16.788	<0.001
Item 18	0.851	0.050	17.084	<0.001
Covariances between				
DR~~CR	0.915	0.023	38.978	<0.001
DR~~CL	0.743	0.042	17.608	<0.001
CR~~CL	0.803	0.056	14.460	<0.001

There was a strong positive correlation between the SSES-TR "debrief and reflection" and "clinical reasoning" subscales (r = 0.749, p <0.001, Table 4). There was a moderate positive correlation between the SSES-TR "clinical learning" and the other two subscales (p <0.001). Participants responded very consistently to the SSSCL items. The SSSCL had a Cronbach's alpha of 0.920 while its subscales "satisfaction with learning" and "self-confidence in learning" had a Cronbach's alpha of 0.888 and 0.849, respectively. Participants had a median SSSCL "satisfaction" and "self-confidence" subscale score of 22 (min-max: 5-25) and 30 (min-max: 10-35), respectively. They had a median total SSSCL score of 4.33 (min-max: 1.25-5.00). Their SSSCL total and subscale scores were weakly and positively correlated with their SSES-TR total and "debrief and reflection" and "clinical reasoning" subscale scores (p<0.05).

Table 4. Correlation between SSES-TR and SSSCL scores

	SSES-TR							
	Debrief and reflection		Clinical reasoning		Clinical learning		Total	
	r*	p-value	r	p-value	r	p-value	r	p-value
SSES-TR								
Clinical reasoning	0.749	**<0.001**						
Clinical learning	0.589	**<0.001**	0.573	**<0.001**				
SCLS								
Satisfaction	0.238	**0.006**	0.219	**0.012**	0.047	0.595	0.211	**0.016**
Self-confidence	0.260	**0.003**	0.141	**0.111**	0.153	0.082	0.207	**0.018**
Total	0.265	**0.002**	0.181	**0.039**	0.114	0.197	0.221	**0.011**

*Spearman correlation coefficient

Reliability: The SSES-TR had a Cronbach's alpha values 0.928, which dropped when the items were removed one by one (Table 5). This was also true for the subscales. The correlation coefficients between the items and scale total and subscale scores ranged from 0.492 to 0.749.

Table 5. Internal consistency of SSES-TR items

	Total Scale		Subscale	
Subscales/Items	**Cronbach Alpha Values***	**CITC§**	**Cronbach Alpha Values****	**CISC§§**
Debrief and reflection				
Item 1	0.921	0.731	0.885	0.711
Item 2	0.922	0.704	0.887	0.692
Item 3	0.925	0.613	0.898	0.583
Item 4	0.923	0.665	0.889	0.656
Item 5	0.922	0.690	0.882	**0.749**
Item 6	0.923	0.647	0.888	0.667
Item 7	0.922	0.717	0.885	0.737
Item 8	0.923	0.653	0.886	0.701
Item 9	0.924	0.624	0.895	0.589
Clinical reasoning				
Item 10	0.922	0.708	0.712	0.620
Item 11	0.926	0.538	0.742	0.521
Item 12	0.924	0.637	0.715	0.598
Item 13	0.927	0.509	0.744	0.534
Item 14	0.924	0.599	0.751	**0.492**
Clinical learning				
Item 15	0.924	0.626	0.759	0.640
Item 16	0.926	0.536	0.738	0.671
Item 17	0.926	0.533	0.764	0.616
Item 18	0.926	0.552	0.776	0.603

Cronbach alpha values: 0.928 for SSES, 0.900 for DR, 0.774 for CR, 0.808 for CL
*Cronbach alpha values of SSES if item deleted **Cronbach alpha values of the corresponding subscale if item deleted
§ Corrected Item-Total Scale Correlation §§ Corrected Item-Subscale Correlation

According to the test-retest reliability results, the SSES-TR total and subscales scores were quite compatible (min ICC = 0.968, Table 5).

Table 6. Test-retest Reliability Results

n=35	**ICC (95% CI)**	**p-value**
SSES Total	0.990 (0.980-0.995)	**<0.001**
Debrief and reflection	0.984 (0.968-0.992)	**<0.001**
Clinical reasoning	0.968 (0.909-0.986)	**<0.001**
Clinical learning	0.981 (0.962-0.990)	**<0.001**

ICC: Intraclass Correlation Coefficient, CI: Confidence interval

DISCUSSION

Education experts argue that satisfaction has a significant effect on academic performance (23). Satisfaction also helps students to increase their knowledge, develop skills, and build self-confidence. It is, therefore, of paramount importance to determine student satisfaction with simulation-based experience. There is, however, only one valid and reliable Turkish scale that can be used to measure student satisfaction with simulation-based experience (11).

A rule of thumb for validity and reliability studies is to have a sample size 5 to 10 times the number of scale items (17). The study sample consisted of 130 participants, which was 7 times the number of the SSES-TR items. Levett-Jones (2011) had recruited 286 students while Williams and Dousek (2011) recruited 167 students (12,24). One hundred and sixty-two paramedic students had been recruited to establish the validity and reliability of the Korean version of the Satisfaction with Simulation Experience Scale (SSES-KR) (25).

The SSES-TR had a CVI of 0.86 while its subscales had a CVI of 0.69 to 1.00. Therefore, no items were removed from the scale. These results show that the SSES-TR has appropriate content and is easy to understand. Confirmatory factor analysis was used for construct validity. Similar to the original scale, the SSES-TR items were loaded to three factors. No item had a factor loading below 0.30 (See Figure 1). Esin et al. recommend that each item have a factor loading of at least 0.30. Therefore, no items were removed. The correlation coefficients between the SSES-TR items and total and subscale scores ranged from 0.492 to 0.749. The SSES-KR was reported to have factor loadings ranging from 0.564 to 0.792 (25).

According to the CFA results, the SRMR and RMSEA were at acceptable levels. RMSEA $\leq$ 0.08, and CFI, GFI, and NNFI $\geq$ 0.90, AGFI $\geq$ 0.80 indicate good fit (26). The CFA results show that the SSES-TR is an appropriate measure that can be used to determine student satisfaction with

simulation-based experience. The SSES-TR also has three subscales, the names of which are the same as those of the original scale; “debrief and reflection,” “clinical reasoning,” and “clinical learning.” However, Williams and Dousek (2012) changed the names of the subscales to “clinical learning and reflection,” “debriefing teamwork and collaboration,” and “clinical reasoning” (24).

Internal consistency was determined using Cronbach's alpha reliability coefficient. Levett-Jones (2011) reported a Cronbach’s alpha of 0.776 for the total scale and 0.850 to 0.935 for the subscales (12). The total SSES-KR was reported to have a Cronbach’s alpha of 0.841 and its subscales were reported to have a Cronbach’s alpha of 0.852 to 0.913 (25). In this study, the total SSES-TR has a Cronbach’s alpha of 0.928 while its subscales have a Cronbach’s alpha ranging from 0.774 to 0.900. A Cronbach’s alpha score of 0.6 to 0.80 indicates “acceptable reliability” while a Cronbach’s alpha score of 0.8 to 1.00 indicates “high reliability” (27). Test-retest was used to assess scale consistency over time. The test-retest method is used to determine how responses to scale items change over time (28). An ICC analysis was used to analyze participants’ responses to the scale items. The results showed that the ICC ranged from 0.968 to 0.990, indicating agreement between the two tests.

CONCLUSION

The SSES-TR is a valid and reliable measure that can be used to evaluate student satisfaction with simulation-based experience. The SSES-TR has subscales similar to those of the original scale. Our results show that the SSES-TR is a highly reliable measure that can be used for the Turkish population. The SSSCL is the scale that is commonly used in Turkey. We, however, believe that the SSES-TR is superior to it because its “debrief and reflection” subscale allows researchers to evaluate student feedback. The validity and reliability of the SSES-TR should be tested on different populations, and the scale should be used in different scenarios.

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RESEARCH ARTICLE

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Effectiveness of Palliative Care Workers in Patient Nutrition

ABSTRACT

Objective: It is important to evaluate the nutrition of patients in palliative care centers. Most patients are unrecognized and lacking treatment, as there is no consensus on ways to scan, diagnose, treat and follow the malnutrition, and the lack of adequate awareness and training of healthcare professionals. This study aims to evaluate the approaches and awareness of healthcare professionals in Turkey who support nutrition in Palliative Care Centers.

Methods: A survey, prepared by researchers, conducted to assess the effectiveness of healthcare professionals in patient nutrition, was conducted on a virtual basis in all healthcare professionals who were fully employed, accessible and volunteered with palliative care patients. The data was evaluated through descriptive and analyzing statistical methods.

Results: The average age of the 105 medical professionals who participated in our study was 36.4±9.3 (25-59), of whom 68 (64.8%) were women and 37 (35.2%) were men. Sixty-seven (63.8%) of the participants, most of whom were physicians, were specialists, 30 (28.6%) were assistants and general practitioners, and 8 (7.6%) were nurses. When asked how many of their patients they started feding products, 38 people (36.2%) said, with 41-60%. If you think you've got enough recognition of nutritional content, there were 28 people who said yes (26.7%), 30 people who said no (28.6%), and 47 people (44.8%) who said sometimes. When asked what they considered the most when planning a feeding product, 95 people (90.5%) said that they cared about the patient's request, compared to the calories and content of the product.

Conclusions: Our study found that participants were largely absent from knowledge and awareness, and observed differences in patient attitudes. Most participants require neutral education and continuity in order to have awareness.

Keywords: Palliative Care, Nutrition, Advanced Cancer.

Palyatif Bakım Çalışanlarının Hasta Beslenmesindeki Etkinliği

ÖZET

Amaç: Palyatif bakım merkezlerinde hastaların beslenmesinin değerlendirilmesi önemlidir. Malnütrisyonun taranması, teşhis edilmesi, tedavi edilmesi ve takip edilmesinin yolları konusunda fikir birliğinin olmaması, sağlık profesyonellerinin farkındalıklarının ve eğitimlerinin eksikliği nedeniyle çoğu hasta tanınmamaktadır ve tedaviden yoksundur. Bu çalışma, Türkiye'de palyatif bakım merkezlerinde hastaların beslenmeyi destekleyen sağlık çalışanlarının yaklaşımlarını ve farkındalıklarını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Sağlık profesyonellerinin hasta beslenmesindeki etkinliğini değerlendirmek için araştırmacılar tarafından hazırlanan anket, palyatif bakım hastaları ile çalışan, erişilebilir ve gönüllü olan tüm sağlık profesyonellerine sanal ortamda uygulandı. Veriler tanımlayıcı ve analiz edici istatistiksel yöntemlerle değerlendirildi.

Bulgular: Çalışmamıza katılan 105 tıp profesyonelinin yaş ortalaması 36,4±9,3 (25-59) olup, 68'i (%64,8) kadın, 37'si (%35,2) erkekti. Çoğunluğu hekim olan katılımcıların 67'si (%63,8) uzman, 30'u (%28,6) asistan ve pratisyen hekim ve 8'i (%7,6) hemşiredir. Beslenme ürününü kendileri başladıkları hasta sayıları sorulduğunda 38 kişi (%36,2) %41-60 oranında yanıt verdi. Besin içeriği konusunda ürünleri yeterince tanındığınızı düşünüyor musunuz ? sorusuna evet diyen 28 kişi (%26,7), hayır diyen 30 kişi (%28,6) ve bazen diyen 47 kişi (%44,8) vardı. Bir beslenme ürünü planlarken en çok neyi düşündükleri sorulduğunda 95 kişi (%90,5) ürünün kalori ve içeriğine kıyasla hastanın isteğini önemsediklerini söyledi.

Sonuç: Çalışmamız, katılımcıların büyük ölçüde bilgi ve farkındalık açısından eksiklerinin olduğunu ve hasta tutumlarında farklılıklar yaşandığını göstermiştir. Katılımcıların çoğu farkındalığın olması için nütrisyon eğitimine ve devamlılığına ihtiyaç duymaktadır.

Anahtar Kelimeler: Palyatif Bakım, Beslenme, İleri Kanser.

INTRODUCTION

Palliative care is an approach that improves the quality of life for patients and their families of patients who face life-threatening illnesses through early detection and effective prevention or remediation of all physical, psychosocial and mental problems, particularly pain (1,2). In palliative care; it is intended to improve the quality of life of patients and their relatives at all times, and to try to ensure better and more peaceful death, which is defined as good mortality to those who enter the terminal period. Palliative care services worldwide are available in a hospital environment, in a home environment, or in hospitals.

Malnutrition is the case in which systemic, metabolic, and mental functional impairments occur by taking macro and micro-nutrient elements less or more than necessary. The diagnosis is made by a comprehensive investigation that includes the patient's anamnesis, history, physical examination, anthropometric and functional measurements, hematological and biochemical markers, and imaging methods. In palliative care patients malnutrition is as important a problem as infection, head injury, and organ failure. Malnutrition rates are reported in the elderly 50-70%, in the neurologic diseases 55-65%, in those with respiratory system diseases 40-50%, in those with inflammatory bowel disease 60-80%, and in those with cancer 65-85% (1). Nutrition approaches in cancer patients vary depending on whether the patient is under oncological treatment or not. Nutrition support syndications and methods are evaluated and determined by the stage of cancer disease, the clinical condition of the patient and the expectation of survival. If patients are under active oncological treatment, diet approaches can increase their tolerance of treatment while maintaining a general condition of the patient (2). Even patients who undergo palliative chemotherapy in advanced cancers can improve their quality of life and contribute to the treatment process. The main purpose of diet approaches in patients with an inactive oncological condition is to prevent premature deaths due to malnutrition and improve quality of life (2). Nutrition support in these patients should be evaluated based on the patient's nutrition level, habits, expectations, and socioeconomic factors. Some of these patients are in a group with severe anorexia, difficulty swallowing, chronic intestinal obstructions (ileus), or lack of oral intake. In terms of maintaining bowel function, in this group of patients, tube feeding methods are the primary option, but with different syndications, parenteral neutralization is also an important part of the support treatment. If the gastrointestinal system is functional, it must always be the first choice as the method to cause more physiological and less complications (3).

As the terminal approaches the term for advanced cancer patients with palliative care, it should be discussed that full nutritional support increases the quality of life due to the lack of treatment of the disease. In the approaches of American oncology guides, palliative care is recommended within 8 weeks of diagnosis for patients who are in the advanced stage or in the forward stage at the time of diagnosis(1). Over 50% of oncology patients have a high incidence of neutral symptoms such as nausea, rapid saturation, and taste changes. In peritoneal attitudes, colorectal and over cancers, retroperitoneal sarcomas can show similar symptoms due to bowel obstructions. Chronic repetitive bowel obstructions and total parenteral neutralization to provide needed nutritional support and relieve symptoms when intestines are not functioning. Parenteral neutralization practices may not affect tumor progression in cases of induction, but may prevent premature mortality due to more malnutrition. Therefore, it is important to detect the malnutrition by screening tests before it reaches the irreversible stage, and to be able to provide nutrition support.

For palliative care patients, the nutrition treatment must be individually adjusted and shaped according to the patient's condition. Malnutrition risk is known to decrease hospitalizations and complications with proper nutrition treatment in patients with high malnutrition or malnutrition (4). A multidisciplinary team approach is important in palliative maintenance services. At the center of this team are close to patients and patients. In general, the world's palliative care team members include doctors, nurses, psychologists, dietitians, physiotherapists, pharmacists, clergy and social workers. In addition, doctors who specialize in other areas of the patient's needs are included (5). In our country, the Ministry of Health has stated that the primary care team should include doctors, nurses, social workers, dieticians and psychologists in the palliative care team (1). For palliative care support to be properly provided, it is necessary to have a good team organization, to have effective collaboration between institutions and disciplines, to train with regular intervals of people, patients, and patient relatives. The choices and decisions of the patient and his family must be respected. What patient needs in-patient support should be evaluated. This study aims to evaluate the methods and patient approaches of healthcare professionals in palliative care and nutritional support..

MATERIAL AND METHODS

Our study is a cross-sectional descriptive survey study. Firstly, after being given permission from the ethics board of the Tepecik Research Hospital at the SBU Izmir Medical School, the pediatric teaching hospital, the assessment of the patient nutrition activities of healthcare professionals with 22 questions was done on a virtual basis with all medical staff members who were working, accessible and volunteered with

palliative care patients. The survey questioned people's social and demographic characteristics, as well as their approach to nutritional support for their patients while working in palliative care services. The identifier and analyzer were evaluated by statistical methods. Fisher or Ki-square test and decision tree methods were used for comparisons. The descriptive findings are presented as mean, standard deviation and frequency distribution number and percentage. Pearson Ki-kare was tested for categorical variables within independent groups.

The CHAID (Chi-squared Automatic Interaction Detection) analysis was performed to classify the occupational group (specialist, assistant and practitioner, nurse) of the participants. CHAID analysis is a method of subgrouping the specified variable (main node) into subgroups of importance according to categories that best describe it.

The selected category is divided into groups by the variable ki-squared test. The division of subgroups is determined by the Bonferroni correction and the p-value calculated. The decision tree has been created based on the criteria of $p<0.05$, the maximum number of levels for CHAID analysis is 3, the number of decision nodes is 10, and the number of terminal nodes is 5. The Statistical significance value of this work has been assumed to be $p<0.05$. The research data was evaluated through the SPSS 23.0 statistical packet program.

RESULTS

The average age of the 105 medical professionals who participated in our study was 36.4±9.3 (25-59), of whom 68 (64.8%) were women and 37 (35.2%) were men. Sixty-seven (63.8%) of the mostly physician participants were specialists, 30 (28.6%) were assistants and general practitioners, and 8 (7.6%) were nutritional nurses. In terms of majors, the highest number of participants were 35 (33.3%), the primary care physician, 34 (32.4%) and the other group as specified (Table 1).

Table 1. Distribution of majors

	Number (N:105)
Practitioner	7
Family Physician	35
Breast Disease Specialist	3
Anesthesiologist	5
Pediatrician	2
Internal Medicine Specialist	3
Oncologist	12
Nurse	4
Others	34

When we looked at the palliative care centers where they worked, the vast majority worked with 79 people, 75.2 percent, in the Palliative Care Centers of the Education Research Hospitals (Table 2).

Table 2. Attendees work in centers

	Number (N:105)	%
Palliative Care Service at the State Hospital	11	10.5
Palliative Care Service at the Education Research Hospital	79	75.2
Palliative Care Service at the University Hospital	10	9.5
Private Hospital or Palliative Care Center	5	4.8

One of the first responses to questions raised by researchers relating to nutrition for patients in attendance services was how much nutrition they started. The maximum response was 41-60% with 38 (36.2%) (Table 3).

Table 3. Rate of feeding product initialization due to patient's malnutrition

	Number (N:105)	%
5-20%	10	9.5
21-40%	11	10.5
41-60%	38	36.2
61-80%	23	21.9
81% and above	23	21.9

Do you talk to your patients for the purpose of informing them about their products at the startup of the feeding product? When asked, 78 people (74.3%) said yes, while others said no, no time, and sometimes I speak. When asked if you think you know nutritional goods well enough, it was 28 people (26.7%) who said yes, 30 people (28.6%) who said no, and 47 people (44.8%) who said yes. Patients who prefer to do their own diet are 38 (36.2%), while 54 (51.4%) respond to patients. Asked 83 people (79 percent) who say yes 11 people (10.5) sometimes, it turns out that the majority can get that kind of support because they want to know how much nutritionist support they can get in the places they work.

Participants were highly likely to warn and educate patients about the risk of aspiration during oral or enteral feeding (84.8%)

What would you recommend for a cancer patient to have calories and liquids at loss of appetite and thirst? Our question was an important one. The maximum response was that 54 people (51.4%) gave parenteral or enteral tubes. Other responders said they had received support from dieticians or experts he worked with (Table 4).

Table 4. Suggestion of calories and fluid intake in advanced loss of appetite and thirst in cancer patients

	Number (N:105)	%
I insist on standard nutrition and fluid intake recommendations	28	26.7
I'd just recommend that he get as much as he can	15	14.3
I try to feed it with parenteral or enteral tubes	54	51.4
Other	8	7.6

Does ethical dilemmas or the reaction of the patient's relatives force you to decide on a terminal-era patient feeding plan? The question is one of the most difficult questions that palliative care decides to feed. 69 (65.7%) of respondents said yes or sometimes.

The proportion of those who recommended probiotics as a supportive product for their patients was 42.9% with 45 people, and the proportion who recommended immunosuppression such as vitamins, zinc and arginine was highest with 60 people, or 57.1%. The number of medics who recommended phytotherapy to their patients was 16 (15.2%) while the number who did not was 89 (84.8%) (Table 5).

Table 5. Patient support product preferences

Would you recommend probiotics as a supporting product?	**Number (N:105)**	**%**
Yes, I do	45	42.9
No, no	23	21.9
Sometimes	37	35.2
Do you recommend immunocurative products such as vitamins, zinc, argias, etc?	**Number (N:105)**	**%**
Yes, I do	60	57.1
No, no	10	9.5
Sometimes	35	33.3
Do you recommend any physiotherapy?	**Number (N:105)**	**%**
Yes, I do	16	15.2
No, no	89	84.8

When asked what they considered the most when planning a feeding product, 95 people (90.5%) said that they cared about the calories and content of the product, while 9 people (8.6%) cared about the patient's request.

When planning feeding methods such as PEG/PEJ, are you having trouble performing the procedure or managing the process afterwards? 25 people (23.8%) answered yes to our question.

66 (62.9%) of patients received support from home health care in nutrition, inspection, treatment and follow-up. Do you think you need nutrition training? 80 people (76.2%) answered yes to our question.

The rate of considering using tele-medicine in dietary follow-up during the pandemic was predominantly no with 75 people (71.4%).

Have your nutrition proposals changed since the pandemic? And when we said, please indicate, we found that vitamin C and vitamin D, hydration proposals were increasing.

When we compared and grouped the answers, we found the value of p in four of our questions in the form of Specialist Physician or Practitioner. Do you plan your own patient nutrition, and those who answered no to our question made sense to the resident and practitioner physicians (p=0.004). If you are familiar with nutritional products as context, the yes answer makes sense for expert physicians (p<0.001). When planning feeding methods such as PEG/PEJ, are you having trouble performing the procedure or managing the process afterwards? the answer to the no question proved to be relevant to specialist physicians (p=0.046). Do you think you need nutrition training? The no answer to his question was meaningful in the direction of specialist physicians (p=0.001) (Table 6).

Table 6. Comparing answers to professional groups

Question 1 -Do you plan your own patient nutrition?				
	Expert	Assistant and Practitioner	Nurse	P
Yes	33(86.8)	3(7.9)	2(5.3)	
No	5(38.5)	6(46.2)	2(15.4)	0.004
Sometimes(by Patient)	29(53.7)	21(38.9)	4(7.4)	
Question 2 - Do you feel you are familiar enough with nutrition products as content?				
	Expert	**Assistant and Practitioner**	**Nurse**	**P**
Yes, I do	21(75)	1(3.6)	6(21.4)	<0.001
No, no	14(46.7)	16(53.3)	0(0)	
Some of them	32(68.1)	13(27.7)	2(4.3)	
Question 3-When you plan nutrition methods such as PEG/PEJ, do you have difficulty getting the procedure done or then managing the process?				
	Expert	**Assistant and Practitioner**	**Nurse**	**P**
Yes	15(60)	10(40)	0(0)	
No	23(76.7)	3(10)	4(13.3)	0.046
Sometimes	29(58)	17(34)	4(8)	
Question 4 - Do you think you need training support for cancer feeding?				
	Expert	**Assistant and Practitioner**	**Nurse**	**P**
Yes	46(0.575)	30(0.375)	4(0.05)	
No	21(0.84)	0(0)	4(0.16)	0.001

Assessed by the classification of professional groups; the majority of people who respond yes to nutrition product recognition (n=28, 26.7%) who say they plan their diet (n=19, 90.5%) are physicians, and sometimes the majority of the professions who respond to no are nurses (n=4, 57.1%), which is statistically significant (p=0,011). Some of them may be identified by their nutritional content, and by no means, the group (n=77, 73.7%) is 65 people who have responded yes or sometimes to their patient plans. The majority of physicians who respond to the questions of sufficient recognition of nutritional products as content have been identified as specialist physicians (n=31, 72.1%), while the majority of those who answer no are residents and practitioners (n=12, 54.5%) (p=0,035). Based on the professional classification performance of the decision tree, the proper classification performance was found to be 67.6%, when the specialist physician was 82.1%, the nurse was 50.0%, the assistant and the general practitioner were 40.0%.

DISCUSSION

Palliative care; Cancer is the field needed in different processes of life in diseases that go with cardiovascular diseases, diabetes, chronic lung, kidney, neurological diseases, and HIV/AIDS. According to statistics from the General Directorate of Public Hospitals at the Ministry of Health, there are 383 palliative care centers in 81 provinces and 5,091 beds in 383 public hospitals in our country. The vast majority of the 105 health workers who participated in our study (75.2%) worked in Palliative Care Centers of Educational Research Hospitals. In palliative care, which requires a multidisciplinary study, 63.8% of our participants were attending physicians, 28.6% were assistants and practitioners, and 7.6% were nutritional nurses. In terms of majors, the largest number of participants were 35 (33.3%), the family physician, and 34 (32.4%), among others.

One-third of patients admitted to palliative care are cancer patients and two-thirds are people with organ failure, infection, neurological illness. Dietary support in cancer patients should be scanned during treatment and follow-up, and it is recommended to start in case of malnutrition (6). The gastrointestinal system is the most physiological way of feeding, and if there are no problems with its operation, the primary enteral feeding path must be preferred. Oral nutrition support (OBD) products include products such as additional meals or snacks to complete nutrition deficiencies for patients at risk of nutrition. Studies have shown in literature to evaluate the effectiveness of OBD use that weight gain and body mass index increase in patients applying OBD is better than those without OBD (5). In our study, the group with the highest proportion of people to start a nutritional product support was a group with 41 to 60 percent of them. 74.3% said they had informed the patient at the start of the working nutrition product. Informing a patient is important for building trust and maintaining product usage.

When asked if you thought you knew nutritional goods well enough, the yes were 26.7 percent. Patients who prefer to do their own dietary planning are 36.2%, while 51.4% have responded to the patient. Respondents were thought to have significantly lower levels of knowledge and awareness regarding the neutral products.

What would you recommend for a cancer patient to have calories and liquids at loss of appetite and thirst? 51.4% of our questions would be parenteral or enteral tube. Other responders said they had received support from dieticians or experts he worked with. In fact, it is advisable that in the terminal period, support for calories and fluid intake is not enforced due to the expected survival of the patient. These and similar ethical dilemmas can be experienced. In our study, do the ethical problems of the participants or the reactions of their relatives force you to make the decision about a nutrition plan in terminally ill patients? 65.7% of respondents answered yes or sometimes. Not eating and drinking is not the cause of death, but part of the normal process of death. Families often get stressed when their loved ones refuse to eat, which is understandable. Families demand artificial nutrition and hydration with false hope, so that they feel that their longevity will improve, their functional status will improve, their comfort and quality of life will increase. In acute cases, these attempts play a significant role in healing, but not in recent dementia, stroke, and terminal-term cancer patients. Reducing fluid support in the near-death patient decreases pulmonary and peripheral edema, acid (7). It is important that palliative care workers be able to tell and understand the role and value of artificial nutrition and hydration in the family (7).

In our study, the rate of recommending immuno nutrition products such as vitamins, zinc, arginine, glutamine was quite high with 60 people (57.1%) who said yes and 45 people (42.9%) who said yes to probiotic products as support. However, 16 (15.2%) who recommended phytotherapy for their patients were extremely small. The effect of arginine and nucleotides in the form of enteral nutrition formulas is studied to support immunization in patients who undergo surgery and radiotherapy. Vitamin D deficiency is very common in cancer patients (8). This deficiency was associated with cancer injection and prognosis (6-8), and a meta-analysis of the randomized controlled study by Bolland and his colleagues showed that the practice of vitamin D±calcium decreased the incidence of patients on skeletal or non-skeletal events by a maximum of 15%. However, it is not yet known whether the use of vitamin D supplements to normalize vitamin D levels should improve prognosis in cancer patients (9). A prospective study of 4459 patients with early

prostate cancer reported a 2.6-fold increase in mortality rates for men who have received a dose of selenium supplement of over 140 mg/day (10). However, it is important to note that supplements of vitamins and trace elements are mandatory if the patient's parenteral nutrition is to last more than a week (11). A study by Talvas and his colleagues also shown that immune cell response increases when arginin is added to enteral nutrition in cancer patients undergoing radiotherapy (12). When the results were analyzed in the review of 15 prospective and retrospective studies that investigated glutamine support in oral mucosia developing in cancer patients undergoing radiotherapy, chemotherapy or chemo-radiotherapy, it was observed that glutamine had positive effects on mucositis in 11 studies, while 4 studies showed no effect (13).

When you plan feeding methods such as Percutan Endoscopic Gastrostomy (PEG)/Percutan Endoscopic Jejunostomy (PEJ), are you having trouble performing the procedure or managing the process afterwards? 25 people (23.8%) answered yes to our question. It is understood that the majority has received support, as 83 individuals (79%) have said yes. In enteral nutrition, oral, gastric, percutaneous and surgical means are used (13,14). In the selection of these ways, it is necessary to take into account indications, contraindications and complications related to the application of these means, as well as good evaluation of the patient (14). Oral nutrition is the first choice in the patient who can take oral and has a good swallowing function. In cases where the oral pathway cannot be used for longer periods of time, more permanent methods are applied. It is indicated in patients who will not be able to switch to oral nutrition within two or three weeks. In our study, we found that healthcare professionals were able to receive an average of support in starting tube feeding for their patients.

Do you think you need nutrition training? 80 people (76.2) answered yes to our question. Meier and Mark. in their study, individuals with advanced life-threatening illnesses and families complained that the quality of care available to them was inadequate and were not satisfied with the service offered (15). In the world, palliative care education is quite different. Palliative care has been recognized as a separate specialty in countries such as the United States, the United Kingdom, Canada and Australia (16). Palliative care is part of clinical education in nursing education in Israel and Jordan (17). Trainings for palliative care workers are refreshable and are recurring on a regular basis; there should be palliative care and training that includes what patients need (18).

When we grouped the answers into Specialist Physician-Assistant or Practitioner-Nurse, we found some meaningfulness in our questions. Do you self-organize your patient nutrition plans, and those who answer no to our question make sense to residents and general practitioners, as measured by the classification of professional groups. The majority of people who respond yes to nutrition product recognition (n=28, 26.7%) who say that they make the dietary plan themselves (n=19, 90.5%) are physicians, and sometimes the majority of those who respond to no are nurses (n=4, 57.1%), which is statistically significant. The group (n=77, 73.7%) who responded in favor of recognizing some of their nutritional content, and 65 people who responded yes or sometimes to the status of preparing sick plans. The majority of physicians who respond to the 65 nutritional questions of adequate recognition as content are qualified physicians (n=31, 72.1%), while the majority of those who answer no are residents and practitioners (n=12, 54.5%).

Based on the professional classification performance of the decision tree, the correct classification performance was found to be 67.6%, with the specialist physician being 82.1%, nurse 50%, assistant and general practitioner 40%. It has been observed that specialist physicians perform professionally in terms of nutrition at a higher rate.

CONCLUSIONS

Awareness and knowledge of patient nutrition may not be enough. Therefore, the need for education arises. . To increase the awareness and awareness of healthcare professionals, conducting simultaneous training for medical professionals in the multidisciplinary team can lead to significant improvements. emergingPalliative care is one of the most common areas of end-of-life care ethical dilemmas. In this respect, ethical decisions can be hard to make Solving these problems should focus on legislative regulation and support from ethical boards. Trainings, planning, support, treatments should be patient- centered and designed to improve patient life comfort.

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RESEARCH ARTICLE

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Quadruple Therapy in Patients with Immune Thrombocytopenia

ABSTRACT

Objective: In the treatment of immune thrombocytopenia dexamethasone, rituximab, and cyclosporine combination therapies provided promising results in recent years. This study aimed to investigate the responses of patients with quadruple therapy which created by combining combinational therapies given in immune thrombocytopenia with eltrombopag.

Methods: Four patients diagnosed with immune thrombocytopenia who received steroid in the first-line treatment and eltrombopag in the second-line treatment without achieving complete remission/partial remission were retrospectively evaluated in terms of the treatment they received and response rates.

Results: received and response rates.

Results:Patients with relapsed/refractory immune thrombocytopenia were treated by oral dexamethasone, oral cyclosporine and intravenous low-dose rituximab in addition to eltrombopag therapy. Eltrombopag treatment was continued at a dose of 50mg/day. No loading dose was given for cyclosporine, weekly blood cyclosporine level was monitored for toxicity and the treatment was titrated to a target dose of 200 to 400 µg/L. No toxicity-induced death, serious treatment-related adverse events, or non-adherence to treatment were observed. The 6-month response rate was 75% and the treatment was well tolerated. Two patients were still followed up by us with a complete response, while one our patient underwent splenectomy because of relapse after 6 months and is still being followed up with eltrombopag therapy. In one our patient, which was unresponsive, romiplastim treatment was applied but there was no response to this treatment either. The patient was referred to a clinical study.

Conclusions: Our study showing that a combination of quadruple therapy can be a treatment option in patients with treatment-resistant immune thrombocytopenia is promising.

Keywords: Immune Thrombocytopenia, Eltrombopag, Quadruple Therapy.

İmmun Trombositopenili Hastalarda Dörtlü Tedavi

ÖZET

Amaç: İmmün trombositopeni tedavisinde son yıllarda deksametazon, rituksimab ve siklosporin kombinasyon tedavileri umut verici sonuçlar vermiştir. Bu çalışmada, immün trombositopenide verilen kombinasyon tedavilerinin eltrombopag ile birleştirilmesiyle oluşturulan dörtlü tedavinin hastalardaki yanıtlarının araştırılması amaçlanmıştır.

Gereç ve Yöntem: İmmun trombositopeni tanısı almış birinci basamak tedavide steroid, ikinci basamak tedavide eltrombopag alan, tam ya da kısmı remisyon sağlanamayan dört hasta retrospektif olarak aldıkları tedavi ve yanıt oranları açısından değerlendirildi.

Bulgular: Relaps /refrakter immün trombositopenisi olan hastalar, eltrombopag tedavisine ek olarak oral deksametazon, oral siklosporin ve intravenöz düşük doz rituksimab ile tedavi edildi. Eltrombopag tedavisine 50 mg/gün dozunda devam edildi. Siklosporin için yükleme dozu verilmedi, haftalık kan siklosporin düzeyi toksisite açısından izlendi ve tedavi 200 ile 400 µg/L'lik bir hedef doza titre edildi. Toksisite kaynaklı ölüm, tedaviye bağlı ciddi advers olaylar veya tedaviye uyumsuzluk gözlenmedi. 6 aylık yanıt oranı %75 idi ve tedavi iyi tolere edildi. Hastalarımızdan iki tanesi halen tam yanıtlı olarak tarafımızca takipli iken bir hastamızda 6.aydan sonra relaps olması nedeniyle splenektomi yapılmış olup halen eltrombopag tedavi ile takiplidir. Yanıtsız olan daha önce splenektomili olan hastamıza ise romiplastim tedavisi uygulandı ancak bu tedaviye de yanıt alınamadı. Hasta klinik çalışmaya dahil edildi.

Sonuç: Tedaviye dirençli immün trombositopenili hastalarda dörtlü tedavi kombinasyonunun bir tedavi seçeneği olabileceğini gösteren çalışmamız umut vaad etmektedir.

Anahtar Kelimeler: İmmun Trombositopeni, Eltrombopag, Dörtlü Tedavi.

INTRODUCTION

Immune thrombocytopenia (ITP) is a disease with an increased risk of hemorrhage developing on an autoimmune basis, which is caused by increased platelet destruction or decreased platelet production, affecting both children and adults (1-3). While it results in complete remission in 80% of children within 3-6 months, it usually becomes chronic in adults (4). The most common symptoms are petechiae and hemorrhage (5). While platelet count is mostly used to evaluate disease status and response to treatment; hemorrhage is the most important factor in clinical prognosis (6), because it has a direct impact on morbidity, mortality, quality of life, and treatment decisions (5). The primary aim of treatment is to obtain an adequate platelet count(7). First- or second-line treatment strategies such as corticosteroids, intravenous immunoglobulin (IVig), and splenectomy may reduce the destruction of antibody-coated platelets, but their efficacy is limited (7). With immunosuppressive monotherapy, ITP patients often require long-term treatment, which sometimes leads to serious adverse effects. Studies involving short-term treatment with dexamethasone and rituximab have reported encouraging results. Adding cyclosporine to this combination targets T cells (8). The purpose of giving combination therapy includes the need for the effects of more rapid-acting agents and synergism between different agents until the effects of rituximab begin (1). The greatest progress in the treatment of ITP in the last decade has been the development of thrombopoietin receptor agonists (TPO-RA) (9). It provides many advantages over other drugs, especially in the elderly population. Comorbidities related to old age affect the course of the disease and responses to treatment (10). Treatment of chronic ITP is difficult, especially because of limited resources and treatment-related complications (11). Therefore, disease management depends on the clinician's decision and patient preference. In this study, we aimed to evaluate the efficacy and safety of the quadruple therapy consisting of oral dexamethasone, oral cyclosporine, and intravenous low-dose rituximab in addition to eltrombopag therapy.

MATERIAL AND METHODS

This study, which was planned retrospectively, included four patients who were diagnosed as having ITP in the hematology department of a tertiary care hospital from January 1, 2013 to December 31, 2020. This study obtained the approval from the ethics committee (Approval Date: 07.04.2021; Reference Number / Protocol No: 2021/07) and was done in accordance with the Declaration of Helsinki. In addition, written informed consent was obtained for all patients participating in the study.

Patients: Four patients who were diagnosed with ITP in our clinic who received IVig + steroid in the first-line treatment and eltrombopag in the second-line treatment, who could not achieve complete remission/partial remission included in the study. Patients with known HIV, hepatitis B or hepatitis C infections, malignant disease diagnosis, chemotherapy or radiotherapy and those with a diagnosis of myelodysplastic syndrome (MDS) or aplastic anemia were excluded from the study. Bone marrow aspiration and biopsy were performed in to rule out MDS and other causes of thrombocytopenia. Response to treatment was evaluated according to the platelet count (/mm³) and defined as complete response (>100,000/mm³), partial response (30,000-100,000/mm³ or doubling of platelet count after treatment), and unresponsive (<30.000/mm³).

RESULTS

IVig (1mg/kg/day iv 2 days) and steroid (dexamethasone 40 mg/day iv 4 days) were given as initial treatment in our four patients. No response was achieved in one of these patients. In the follow-up of our patients who responded to therapy, loss of response occurred in one of patient at the 3rd month, and in the other patients at the 6th and 12th months, and they were readmitted to the hospital with hemorrhage. The treatment with IVig and steroids was repeated in these patients. However, no response was achieved. Splenectomy could not be performed in two of our patients due to their age. One of our patients voluntarily refused to have splenectomy. One of our patients had a splenectomy due to ITP in childhood. Eltrombopag treatment was started in our patients who were unresponsive to steroid treatment and could not undergo splenectomy. The initial dose of eltrombopag was 50 mg; it is given as a recommended dose by the Turkish Ministry of Health. After 2 weeks of treatment, in those with platelet levels <30.000/mm³ the dose was increased 25 mg up to a maximum daily dose of 75 mg. However, no response was achieved. We added oral dexamethasone (40 mg/day 4 days), oral cyclosporine (2.5-3 mg/kg/day 28 days), and intravenous low-dose rituximab (100 mg/day iv 7, 14, 21, 28 days) to the eltrombopag 50 mg/day treatment. We did not give a loading dose for cyclosporine, we monitored weekly blood cyclosporine level for toxicity and titrated to a target dose of 200 to 400 μg/L. The demographic and clinical characteristics of our patients are shown in Table 1. No toxicity-induced death, serious treatment-related adverse events, or nonadherence to treatment were observed. The responses of the patients were summarized graphically in Figure-1.

Overall, the complete response rate at 6 months was 75% with quadruple therapy. In our 3 patients who received quadruple therapy partial

Table 1: Demographic and clinical characteristics of the patients.

Factors	Case-1	Case-2	Case-3	Case-4
Age/sex	51/male	68/female	58/female	32/female
Previous treatment	Methylprednisolone +IVig No splenectomy Eltrombopag	Methylprednisolone +IVig No splenectomy Eltrombopag	Methylprednisolone +IVig No splenectomy Eltrombopag	Methylprednisolone +IVig splenectomy Eltrombopag romiplostim
Bone marrow biopsy	(+)	(+)	(+)	(+)
Time from First Diagnosis to Quadruple therapy (TT4+eltrombopag)	12th month	3rd month	6th month	-
Response to Quadruple therapy (TT4+eltrombopag)	Complete response	Complete response	Complete response	No response
The final response status	after TT4+eltrombopag treatment was sustained with eltrombopag 50mg/day. Eltrombopag treatment was discontinued in the 24th month. The follow-up of the patient is continuing without medication.	after TT4+eltrombopag treatment was sustained with eltrombopag 50mg/day. The patient is still using eltrombopag 50mg/day PO.	Splenectomy (+) due to loss of response 6 months after the response to TT4+eltrombopag treatment. Currently using eltrombopag 50 mg po	No response She was referred to a clinical study.

IVig:Intravenous immunoglobulin; TT4: high-dose dexamethasone, low-dose rituximab, and cyclosporine; po:peroral

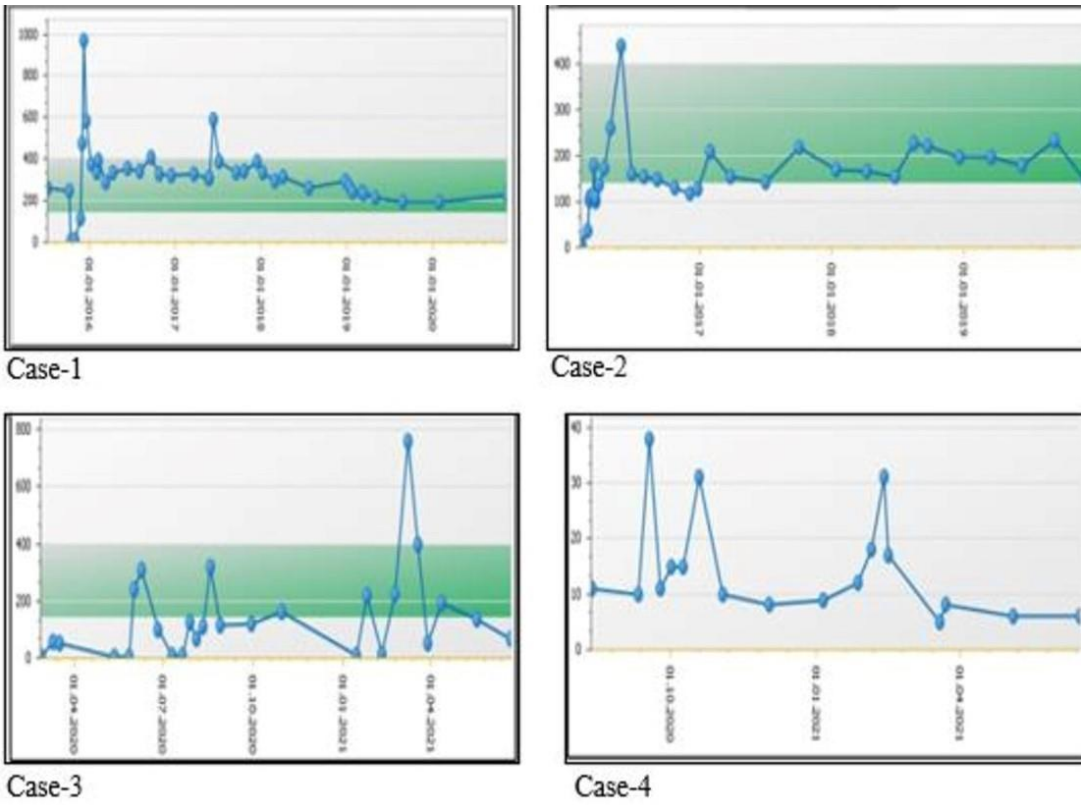

Figure 1. Graphs showing the responses achieved with quadruple therapy.

response (platelet 30000-100000/mm³) was achieved on the 14th day and complete response (>100000/mm³) was achieved on the 28th day. While our case-1 and case-2 patients are still being followed up by us with a complete response as of 2022, case-3 underwent splenectomy because of relapse after 6 months and is still being followed up with eltrombopag therapy. In case 4, which was unresponsive, romiplastim treatment was applied with an off-label application, but there was no response to this treatment either. The patient was referred to a clinical study.

DISCUSSION

The interpretation of our study is limited due to the small number of cases. Bone marrow examination is not diagnostic in patients with ITP, but it is recommended to be performed in patients with hematologic abnormalities and those who do not respond adequately to treatment (12). We also performed bone marrow aspiration and biopsy in our patients to exclude MDS and other hematologic pathology. Quadruple therapy was well tolerated by 4 of our patients, including the one who is over 65 years of age. Most of the treatment-related adverse events were grade-I and usually resolved in a short time. Excessive toxicity was not observed. Our study included 4 patients who had failed previous treatments (steroid, eltrombopag, splenectomy in one patient). Steroid resistance had increased significantly in all 4 patients who had previously received 2 lines of treatment. All of these cases were less likely to respond or recover spontaneously than previously untreated ITP patients (13,14). Although treatment with quadruple therapy was more successful in patients who failed <3 steps of treatment, longer duration of the disease was not a disadvantage; however, one of our patients did not respond to the treatment. Since CD4+ T cell activation is part of the pathogenic cycle that perpetuates ITP, suppressing their activation seems a resonable goal. Supportive of this hypothesis, cyclosporine monotherapy has been shown to be effective in chronic and refractory ITP (15). Rituximab (RTX), a chimeric monoclonal antibody against CD20, has been frequently used in the management of ITP and has been recommended as second-line therapy (1). Over the past decade, clinical trials on RTX have reported an initial response rate of 50-60% in ITP (16). Recent studies have shown that the response rate to low-dose RTX 100 mg once weekly for 4 weeks is similar to that of standard-dose RTX (375 mg /m² x 4) in ITP patients (17). Choi et al (8) reported in their study that platelet counts increased within 4 weeks after the start of treatment, and CD4+ counts decreased during this period. Although dexamethasone alone may cause T-cell suppression to a certain degree, they hypothesized that there might be a synergism with cyclosporine that may result in improved platelet responses, at least for a subset of ITP patients. Hanyin Wang et al (18) reported that they treated a 29-year-old male patient with severe ITP refractory to standard therapy, including steroid, IVig, and then splenectomy by using combination therapy of rituximab, romiplostim, and mycophenolate. Future studies are needed to evaluate the safety and efficacy of combining rituximab with TPO-RAs, and immunosuppression therapy in the postsplenectomy setting particularly for patients with refractory ITP. The response delay reported with low-dose rituximab can be improved by adding dexamethasone (15). In the study of Choi et al(8) the important advantage of TT4 (high-dose dexamethasone, low-dose rituximab, and cyclosporine) was that it provided long-term remission in 60% of the patients in a short time (28 days) without further treatment, and thus the results of the study were promising. Romiplostim and eltrombopag, which are TPO-RA, are increasingly used in the treatment of ITP. Previous studies have shown that both drugs are generally effective and safe in most ITP patients. However, serious adverse events such as thromboembolic events, arthralgia, increased bone marrow fibrosis, and myeloproliferative neoplasms have also been reporte d(19). Ahmad F et al (11) reported that TT4 was successful in their study that included 40 patients and the 6-month response rate was high. In several recent studies 375mg/m² weekly treatment of rituximab in combination with dexamethasone for 4 days has been shown to increase platelet counts in chronic ITP patients but not the risk of adverse effects. This combination is associated with higher platelet counts compared to dexamethasone monotherapy (18). Ahmad F et al(11), like Choi et al (8) suggested that lower doses of 100 mg weekly rituximab for 4 weeks may be beneficial for chronic ITP patients. Patient management is dependent on clinician decision and patient preference, given both the rarity of the condition and the lack of high-quality clinical trial evidence to inform practice guidelines. Based on these studies, we have also given TT4 treatment together with eltrombopag in our patients.

CONCLUSION

We found that the responses were long-term in three of our four cases. Our literature search revealed that this type of combination therapy is unique. Although our case number is low, our experience has shown that quadruple therapy can also be used as an option in ITP patients who are resistant to treatments. To assess the effectiveness and long-term results of this new combination treatment, prospective studies with a large number of cases are needed.

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RESEARCH ARTICLE

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Ocular Findings in Rheumatoid Arthritis: Retrospective Study

ABSTRACT

Objective: The aim of this study is to determine the frequency of the accompanying ocular findings in Rheumatoid Arthritis (RA) patients.

Methods: Patients who were consulted at the eye clinic with the diagnosis of rheumatoid arthritis between 01 March 2017 and 28 February 2022 were included in the study. The patients' files were reviewed retrospectively from the hospital information method system, and the demographic characteristics of the patients and eye examination findings related to rheumatoid arthritis were recorded.

Results: The records of 23840 patients who were consulted to the eye clinic with the diagnosis of rheumatoid arthritis were reviewed retrospectively, and 2691 patients who were seropositive as a result of the examination were included in the study. Anterior segment biomicroscopy, Schirmer test, tear break-up time (BUT) and fundus examination findings of the patients were evaluated in terms of ophthalmological examination. Of all the patients, 2067 were female and 624 were male. The majority of the patients were between the ages of 41 and 65, with 1374 females and 421 males. While the most common finding of ocular involvement due to rheumatoid arthritis was the lack of tears, known as dry eye, with a rate of 25.97%, episcleritis was found in 4.57% of the patients and scleritis in 1.37%.

Conclusions: Rheumatoid Arthritis is a systemic disease that can progress with extra-articular findings and may even appear as its first finding, and may be accompanied by ocular findings at a rate that may impair the quality of life of the patients. A holistic approach in patients with rheumatoid arthritis will positively affect the prognosis of the disease and patients' quality of life in terms of eye health, as is common in chronic diseases in the community.

Keywords: Rheumatoid Arthritis, Eye, Scleritis, Episcleritis.

Romatoid Artritte Göz Bulguları: Retrospektif Çalışma

ÖZET

Amaç: Bu çalışmanın amacı, Romatoid Artrit (RA) hastalarında eşlik eden göz bulguları sıklığını incelemektir.

Gereç ve Yöntem: Çalışmaya 01 Mart 2017 ile 28 Şubat 2022 tarihleri arasında romatoid artrit tanısıyla göz kliniğine konsülte edilmiş olan hastalar dahil edilmiştir. Hastaların dosyaları hastane bilgi yöntemi sisteminden retrospektif olarak incelenerek hastaların sistemde kayıtlı olan demografik özellikleri ve romatoid artrite bağlı olan göz muayenesi bulguları kayıt altına alınmıştır.

Bulgular: Romatoid artrit tanısıyla göz kliniğine konsülte edilen 23840 hastanın kayıtları retrospektif olarak incelenmiş olup, inceleme sonucunda seropozitif olan 2691 hasta çalışmaya dahil edilmiştir. Hastaların oftalmolojik muayene açısından ön segment biyomikroskopisi, Schirmer testi, gözyaşı kırılma süresi (BUT) ve gözdibi muayenesi bulguları değerlendirildi. Hastaların 2067'si kadın 624'ü erkek idi. Hastaların büyük çoğunluğu 41-65 yaş arasında olup, 1374'ü kadın, 421 ise erkek idi. Romatoid artrite bağlı olarak en sık görülen oküler tutulumun bulgusu %25,97 oranıyla kuru göz olarak bilinen gözyaşı eksikliği iken, hastaların %4,57'sinde episklerit, %1,37'sinde ise sklerit bulgsu saptanmıştır.

Sonuç: Romatoid Artrit eklem dışı bulgularla seyredebilen ve hatta ilk bulgusu olarak da ortaya çıkabilen sistemik bir hastalık olup, hastaların yaşam kalitesini bozabilecek oranda göz bulguları eşlik edebilir. Toplumda sık görülen kronik hastalıklarda olduğu gibi romatoid artrit hastalarında bütüncül bir yaklaşım hastalığın prognozu ve hastaların göz sağlığı açısından yaşam kalitesini olumlu etkileyecektir.

Anahtar Kelimeler: Romatoid Artrit, Göz, Sklerit, Episklerit.

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune systemic inflammatory disease, and the etiology is still unknown. There are many different theories on etiopathogenesis. RA does not only cause arthritis, but also many extra-articular findings such as neuropathy, pericarditis, glomerulonephritis, major cutaneous vasculitis, ocular manifestations, and different types of vasculitis (1). Extra-articular manifestations in RA are present, particularly in 10-20% of seropositive patients (2). Ocular manifestations are dry eye, corneal changes, episcleritis, scleritis, and retinal vasculitis in order of frequency. The most common and often the first ocular finding in patients with RA is dry eye. Episcleritis is usually a self-limiting, recurrent inflammatory disease that affects the episcleral tissue located between the conjunctiva and the sclera. Although there may be an underlying systemic disease in one-third of cases, most of them are idiopathic (3). On the contrary, scleritis is a more serious condition. It is a potentially blinding inflammatory disease which is defined by edema and cellular infiltration of scleral and episcleral tissues due to intense inflammation. Scleritis is of two types, anterior and posterior. Anterior scleritis can be nodular, diffuse, necrotizing with inflammation (necrotizing), and necrotizing without inflammation (scleromalacia perforans) (8). The most common clinical conditions are nodular scleritis and diffuse scleritis. Necrotizing scleritis, which may be inflammatory or non-inflammatory, is even less common. Its clinical course is poor and is often associated with autoimmune disorders. Posterior scleritis is defined by retrobulbar edema, thickening of the posterior layers of the eye (choroid and sclera), and flattening of the posterior surface of the globe edema (4).

Peripheral corneal disorders are much more common in patients with RA. Rarely, severe corneal changes such as sclerosing keratitis, peripheral corneal thinning, acute corneal lysis, and acute stromal keratitis may occur. Vasculitis may develop in approximately 1% to 5% of patients with RA (3). Retinal vasculitis usually affects the terminal branches of arteries and veins in the periphery of the retina. The aim of this study is to reveal the different ocular findings and their ratio in RA.

MATERIAL AND METHODS

The study was carried out in Gulhane Training and Research Hospital of the Ministry of Health, following the criteria of the Declaration of Helsinki, after obtaining the necessary permissions from the Health Sciences Gulhane Ethics Committee. In the period of 2017-2022, patient records in ophthalmology outpatient clinic were reviewed and all diagnoses that could be related to RA were evaluated. A total of 23840 patient records with RA and possibly associated diagnoses were detected. Patients aged 18 years and over and diagnosed with seropositive RA were included in the study. The entity of Rheumatoid factor (RFIgM) in the serum was measured with standard test methods based on the agglutination principle in the Immunology Laboratory of our hospital. All patients were found seropositive. Ophthalmological examination (biomicroscopy, tear break-up time (BUT), Schirmer test, and fundus examination) findings obtained from the hospital information management system were recorded.

RESULTS

The records of 23840 Rheumatoid Arthritis and related patients who were consulted with the eye clinic were reviewed. From these patient records, 2691 patients, especially those diagnosed with seropositive Rheumatoid Arthritis, were evaluated in detail within the study. Ophthalmological examination findings obtained from the records, in particular, anterior segment biomicroscopy, BUT, Schirmer test,and fundus examinations of the patients were assessed. 2067 of the patients were female and 624 were male. Regarding the mean age, the majority of those were between the ages of 41-65 with 1795 people (1374 women, 421 men). While the most common sign of ocular involvement was lack of tears (dry eye) (rate 25.9%), episcleritis was found in 4.6% and scleritis in 1.37%. There were no patients with necrotizing scleritis, scleromalacia or retinal vasculitis of the cornea was not detected in our patients.

Age and gender of all seropositive patients evaluated in the eye clinic are presented as follows: Table 1. It is found that the frequency of RA is highest between the ages of 41-65 and it is much more common in women than men.

Table 1. Age and gender of patients with ocular manifestations of RA

Age (year)	Male (n)	Female (n)	Total (n, %)
20-40	68	284	362 (13.4)
41-65	421	1374	1795 (66.7)
>65	149	464	534 (19.8)

Among the 2691 patients examined, ocular symptoms were present in 859 patients (31.9%) (Table 2). Dry eye was found in 25.9% of these patients, episcleritis in 4.6%, and scleritis in 1.37%. Scleritis, one of the eye findings of RA, can have various conditions such as nodular, diffuse, and necrotizing. When the frequency of the forms of scleritis was evaluated in our patients, it is found that they were mostly in nodular form and no necrotizing form was found.

Table 2. Ocular findings in patients with RA

Ocular findings	The number of patients (n, %)
Dry eye	699 (25.9)
Episcleritis	123 (4.6)
Scleritis	37 (1.4)

Dry eye was present in 699 patients which means 25.9% of all patients. Episcleritis was detected in 123 (4.57%) patients, and scleritis was detected in 37 (1.37%) patients. When all patients were examined, no patient with posterior or necrotizing scleritis was observed. Similarly, no retinal vasculitis was diagnosed in our patients.

DISCUSSION

RA, a systemic inflammatory chronic disease of unknown origin, primarily impacts peripheral joints symmetrically. Although there are many theories about its pathogenesis, most scientists support the theory that rheumatoid factor (RF) was discovered based on immunology. RF is an antiimmunoglobulin formed against the Fc fragment of the human IgG molecule. Presumably, B lymphocytes produce autoantibodies (i.e. [RFs]), while CD4 T cells, mononuclear phagocytes, neutrophils, osteoclasts, and fibroblasts, which play important cellular roles in the pathophysiology of RA, contribute to aberrant release of various chemokines, cytokines, and other inflammatory mediators shown in RA patients. RF may be existing in other inflammatory disorders and may be existing in healthy individuals and therefore, is not a pathognomonic manifestation of RA. The other main theory is genetics. HLA-DR 4/DR 1, an important genetic factor of RA, is present in up to 90% of patients with RA. Moreover, genetic features and immune system defects have influence on the development and the spread of the disease. Inflammation and overgrowth of the synovium damage some tissues, including ligaments, tendons, cartilage, blood vessels, and bone. (1). Extra-articular effects of organs such as the lungs, skin, eyes, and heart is significant and is found in 10-20% of patients, more common in seropositive patients (2). In our study, the most frequent finding of ocular involvement was dry eye with a rate of 25.9%. The occurrence of dry eye in the literature ranges from 11.6% to 50% (3). Dry eye in RA is classically described as keratoconjunctivitis sicca. Patients with dry eye need lifelong artificial tear supplementation. Occasionally, disease-modifying antirheumatic drugs (DMARDs) and systemic immunosuppressive agents such as Cyclosporine A or a monoclonal antibody to TNF-alpha such as infliximab may be required to resolve severe symptoms and to improve tear production and (4,11). In our study, episcleritis was diagnosed in 123 patients. In most cases, no treatment was required. Inflammation is localized in the superficial episcleral vascular network and, when examined histopathologically, shows vascular dilatation, perivascular infiltration, and non-granulomatous inflammation. There are two clinical types of episcleritis: simple and nodular. The most frequently observed type is simple episcleritis with recurrent bouts of moderate or severe inflammation, usually at intervals of 1 to 3 months. Attacks usually last 7-10 days and most resolve after 2-3 weeks. Simple episcleritis usually does not require treatment. Artificial tears are helpful for patients with mild to moderate symptoms. Prolonged attacks may be more frequent in patients with systemic conditions. Some patients report that attacks are more common in the spring or autumn. Patients suffering from nodular episcleritis typically have prolonged episodes of inflammation that are more painful than simple episcleritis (5,6,11). The use of artificial tears may be beneficial for patients with mild symptoms. Nodular episcleritis has the potential to accompany a systemic disease. Patients with severe or prolonged attacks may require artificial tears, topical corticosteroids, or anti-inflammatory agents. Topical 0.5% prednisolone, 0.1% dexamethasone or 0.1% betamethasone can be used every day in those patients. Systemic anti-inflammatory agents may also be helpful if nodular episcleritis does not respond to topical therapy. Flurbiprofen (100 mg daily) is usually effective until the inflammation is decreased. It was reduced to 75 mg per day upon response. If there is no response to the first line flurbiprofen, indomethacin should be used. As a rule, a patient who does not respond to any nonsteroidal anti-inflammatory agent (NSAID) may react to another NSAID (7,8).

Scleritis is a much more serious condition. Therefore, accurate and prompt diagnosis is important Immediate initiation of appropriate systemic therapy can halt disruption of both ocular and systemic processes, thereby avoiding globe destroying and prolonging survival. (9). Scleritis is classified into anterior and posterior scleritis. The most frequently observed clinical forms of anterior scleritis are diffuse scleritis and nodular scleritis. It can also occur as inflammatory necrotizing scleritis with inflammation and non-inflammatory necrotizing (scleromalacia perforans) scleritis without inflammation. Although necrotizing scleritis with or without inflammation is rare, the prognosis is much worse, and it is often related with systemic autoimmune disorders. Posterior scleritis, on the other hand, is characterized by flattening of the posterior surface of the eyeball, thickening of the posterior layers of the eye (choroid and sclera), and retrobulbar edema. Ocular complications of scleritis may result in vision loss and eye damage because of prolonged scleral inflammation. Uveitis (approx. 42%), peripheral ulcerative keratitis (13-14%), glaucoma (12-13%), cataract (6-17%), and fundus abnormalities (approx. 6.4%). These conditions are most frequent in necrotizing scleritis, which is the most devastating type of scleritis (11,12). Like the literature studies, 1.7% of all patients had scleritis in this study and anterior scleritis was detected in all of them. The first finding detected was conjunctival hyperemia, which could be localized or involve the entire sclera, most commonly in the interpalpebral region. In the examination, it is an important sign that the redness

does not go away after topical applications of routinely used sympathomimetic dilatation agents. Other symptoms of scleritis are watering, photophobia, pain, and tenderness. In the biomicroscopic examination of the eye, the maximum effect is in the deep episcleral mesh and some in the superficial episcleral mesh. Treatment of scleritis requires regular therapy such as non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) or corticosteroids (5,13). Posterior scleritis or scleromalacia of the cornea were not detected in the observed patient group. Retinal vasculitis is one of the ocular signs of RA. It affects approximately 1% to 5% of patients with established RA (1,14). Retinal vasculitis is commonly located at the periphery of the retina, involving peripheral branches of veins and arteries. Treatment includes topical corticosteroid, NSAIDs, systemic corticosteroid, and biologic therapy (15,16). Recent studies indicates that new biotechnological treatments such as rituximab provide important efficacy and safety (17-19). Biological therapy in rheumatoid arthritis requires treatment with DMARDs, including ocular signs such as keratoconjunctivitis sicca and retinal vasculitis (20-22).

CONCLUSION

Extra-articular organ involvement is a significant issue in RA as they may cause damage in affected organs. Extra-articular complications include ophthalmologic manifestations, which in some cases may be the first sign of the disease. Ocular manifestations of RA are dry eye and inflammatory ophthalmologic conditions such as scleritis corneal changes, episcleritis, and retinal vasculitis. The main cause of necrotizing scleritis and peripheral ulcerative keratitis is RA. These are the two most severe ocular conditions related with the disease, and these conditions greatly affect the prognosis, especially due to their relation with systemic vasculitis, even mortality. As a result of that, ophthalmologists should cooperate closely with rheumatologists in the diagnosis, treatment, and follow-up of patients with RA.

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RESEARCH ARTICLE

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Being a Medical Student in the Shadow of a Pandemic: Psychological Reactions of Medical Students in the COVID-19 Pandemic and Their Views on Online Learning

ABSTRACT

Objective: In this study, it is aimed to determine the psychological reactions of pre-clinical medical school students to the COVID-19 pandemic and their views on online learning.

Methods: A cross-sectional study was conducted on 722 medical students. Data were collected with an online questionnaire between 20 and 27 December 2020. A data collection form including questions about sociodemographic characteristics, opinions about online learning, the Impact of Event Scale-Revised, and the Insomnia Severity Index scales was used.

Results: The mean age of the participants was found to be 20.7±1.6 years. 393 (54.4%) of them were women. 671 (92.9%) of the students stated that they were concerned about the disruption of their education due to the pandemic, and 76.3% (n=551) preferred the face-to-face education environment in their schools to the online learning environment. Of the students, 181 (25.1%) had symptoms of post-traumatic stress disorder (PTSD) and 171 (23.6%) had symptoms of insomnia. The probability of posttraumatic stress disorder was higher in women than in men (OR=1.489, 95% CI=1.02-2.16; p=0.038). In those who have relatives who have contracted COVID-19, compared to those who have not (OR=1.489.95% CI=1.02-2.16; p=0.038), and those with an increased fear of COVID-19 transmission to their relatives were less likely to have PTSD symptoms than those with or without (OR=0.523, 95% CI=0.339-0.807; p=0.003). In addition, those who followed the news about COVID-19 from social media were more likely to have symptoms of PTSD in October than those who followed it from other sources (OR=0.662, 95% CI=0.461-0.951; p<0.001). The probability of PTSD symptoms was significantly higher in students who had high anxiety about the disruption of their education due to the pandemic than in those who had little or no (OR=1.310, 95% CI=1.111-1.543; p=0.001).

Conclusions: Medical students are experiencing the psychological effects of the pandemic and are seriously concerned about the disruption of their education.

Keywords: Medical Student, Online Learning, Post-Traumatic Stress, Insomnia, COVID-19 Pandemic.

Pandeminin Gölgesinde Tıp Öğrencisi Olmak: Tıp Öğrencilerinin COVİD-19 Pandemisine Karşı Psikolojik Tepkileri Ve Uzaktan Eğitimle İlgili Görüşleri

ÖZET

Amaç: Bu çalışmada, preklinik dönem tıp öğrencilerinin Covid-19 pandemisine karşı psikolojik tepkilerinin ve uzaktan eğitimle ilgili görüşlerinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Gönüllü 722 öğrenci ile kesitsel bir çalışma yapıldı. Veriler 20-27 Aralık 2020 tarihleri arasında, çevrimiçi bir anket aracılığıyla toplandı. Veri toplama aracı olarak sosyodemografik bilgiler ve uzaktan eğitimle ilgili görüşlere yönelik bir soru formu, Revize Olayların Etkisi Ölçeği ve Uykusuzluk Şiddeti Ölçeği kullanıldı.

Bulgular: Katılımcıların yaş ortalaması 20,7±1,6 ve 393'ü (54,4%) kadındı. Öğrencilerin 671'i (92,9%) eğitimlerinin aksaması ile ilgili kaygılandığını, %76,3'ü (n=551) okullarındaki eğitim ortamını uzaktan eğitim ortamına tercih ettiğini belirtti. Öğrencilerin 181'inde (25,1%) travma sonrası stress hastalığı (PTSD) semptomları, 171'inde (23,6%) uykusuzluk semptomları bulunmaktaydı. Travma sonrası stres hastalığı olasılığı kadınlarda erkeklere göre (OR=1.489, 95% CI=1.02-2.16; p=0,038) daha fazlaydı. Covid-19'a yakalanan akrabası olanlarda olmayanlara göre (OR=1.489, 95% CI=1.02-2.16; p=0,038), yakınlarına Covid-19 bulaşma korkusu fazla olanlarda az olan veya olmayanlara göre (OR=0.523, 95% CI=0.339-0.807; p=0.003) PTSD semptom olasılığı daha fazlaydı. Ek olarak, Covid-19 ile ilgili haberleri sosyal medyadan takip edenler öğrencilerde diğer kaynaklardan takip edenlere göre (OR=0.662, 95% CI=0.461-0.951; p<0,001 PTSD semptom olasılığı daha yüksekti. Eğitimlerinin aksaması konusunda kaygıları fazla olan öğrencilerde, az olan veya olmayanlara göre PTSD semptom olasılığı anlamlı şekilde daha yüksekti (OR=1.310, 95% CI=1.111-1.543; p=0,001).

Sonuç: Tıp öğrencileri pandeminin psikolojik etkilerini yaşamakta, eğitimlerinin aksaması konusunda ciddi olarak kaygılanmaktadırlar.

Anahtar Kelimeler: Tıp Öğrencisi, Uzaktan Eğitim, Travma Sonrası Stres, Uykusuzluk, Covid-19 Pandemisi.

INTRODUCTION

We are witnessing an extraordinary period in which a disease that first appeared in Wuhan, China, on 31 December 2019 and spread rapidly, paralyzed life all over the world (1). The World Health Organization defined this disease as COVID-19 and declared it a global pandemic on 11.03.2020 (2). On the same date, the first COVID-19 case was seen in Turkey (3). At the time that this article was written the number of cases in Turkey exceeded 2 million, and nearly 20 thousand deaths occurred (4).

Since the beginning of the pandemic, everything has changed rapidly in the globalizing world. The COVID-19 pandemic had profound effects on social, cultural, economic, and other areas of life, especially health and education (5). Education was interrupted at all levels first, followed by online learning (OL). However, neither students nor trainers had OL experience. In this process, uncertainties about how education will be, how exams will be held, how long the restrictions and changes made due to the pandemic will last, as well as economic problems, the increasing number of COVID-19 cases and deaths negatively affected the psychological state of medical students and all segments of the society. All these developments bring along various mental health issues and insomnia (6).

The Covid-19 pandemic has created a state of fear all over the world. The large number of unknowns related to the disease, the lack of an effective vaccine or treatment, its rapid spread, causing death, mask and social distancing practices, quarantine and restrictions have caused various psychological problems in all parts of society for reasons such as (7).

It has been predicted that the pandemic will create a global crisis in terms of community mental health and will have more severe consequences for public health in the long term than the effects of infection (8, 9).

Medical students, doctors of the future, closely monitored this whole process and, naturally, were impressed. In addition to the factors mentioned above, factors such as the evacuation of university campuses, online training and exams, disruption of practical training, frequent use of social media as a source of socialization and information acquisition, increased screen activities, uncertainty in medical students have further increased these problems.

Studies show that university students are vulnerable to psychological problems in the pandemic, and online learning, quarantine, and restrictions have a significant impact on students' anxiety levels (10). In a study, it was suggested that the psychological consequences that develop due to the pandemic in students may be serious, and psychological interventions are necessary to reduce the stress that students feel and improve their sleep quality (11). The stress caused by the pandemic is an important factor for insomnia. Studies have shown that insomnia is 3 times more common in people who experience severe stress. On the other hand, both stress and insomnia also interfere with learning (12). Zhou et al.in the study, it was found that 25.7% of university students experienced sleep problems during the COVID-19 pandemic process (13).

Post Traumatic Stress Disorder (PTSD) is a constant state of arousal and alertness after an event that causes severe stress. Activation of the hypothalamic-pituitary-adrenal axis due to stress experienced during traumatic events leads to insomnia. For this reason, PTSD is closely related to sleep disorders. In PTSD, difficulty falling asleep, frequent waking up at night, daytime drowsiness are frequent. The increase in cortisol due to insomnia makes it a vicious circle. Conversely, sleep disorders also affect mental health and cause stress and a vicious circle in the process (14, 15).

Although many studies have been conducted from different countries on the effects of the pandemic on the mental health of various population segments, studies about the psychological impact and the needs of medical students are relatively limited. These studies are usually studies related to mental problems such as anxiety, anxiety, stress, depression, burnout (16-19). Studies focusing on insomnia and PTSD in medical students are relatively limited (11, 13). In our study, it is aimed to investigate the psychological effects of the Covid-19 pandemic on medical students with insomnia and PTSD symptoms and to determine the opinions of students about online learning. The questions of our research are as follows:

1. How often are PTSD symptoms and insomnia Dec the pandemic period among medical students and what are the associated factors?

2. What are the opinions of medical students about online learning?

MATERIAL AND METHODS

Ethical Consent: Ethical permissions were taken from the Atatürk University Clinical Research Ethics Committee (IRB Number: B.30.2.ATA.0.01.00-10/14, Date: 17.12.2020). The study was carried out per the rules of the Helsinki Declaration.

Study Setting and Participants: This is a cross-sectional study performed on the preclinical students of Atatürk University Faculty of Medicine between 20 and 27 December 2020. Participation in the study was provided voluntarily. No printed material was used due to pandemic conditions. The data was collected through an online questionnaire prepared by the authors. It was sent to the students via e-mail, WhatsApp, and other social media accounts. Students were informed about the purpose of the study and invited to participate in the online survey. The first item of the survey was "I accept to participate in the study voluntarily." Thus, online informed consent was achieved. A total of 962 students studying in grades 1, 2, and 3 were invited to participate in the survey. As a result, 722 students responded, making 75% of the population.

Data Collection Tools: A questionnaire composed of four sections was used for data collection:1) sociodemographic characteristics 2) views on online learning 3) The Impact of Event Scale-Revised, and 4) the Insomnia Severity Index.

The Impact of Event Scale-Revised (IES-R): It is a 22-item scale developed by Weiss and Marmar to measure the level of post-traumatic stress and used in community surveys (20). The scale uses a 5-point Likert scale ranging from not at all (0) to extremely (4). Total scores are between 0 and 88. The Turkish adaptation of the scale was performed by Corapcıoglu et al. (2006) (21). Accordingly, a score ≥33 shows that the person's level of stress is high. We calculated the Cronbach alpha value of IES-R as 0.92.

Insomnia Severity Index (ISI): The Insomnia Severity Index (ISI) is a scale developed by Morin (2011) to determine the severity of insomnia symptoms (22). Its Turkish adaptation was performed by Boysan et al. (2010) (23). The scale consists of seven items scored on a 5-point Likert system, ranging from 0 to 4. The total scale

scores can range between 0 and 28. While 0-7 points indicate insignificant insomnia, 8-14 points are categorized as clinical insomnia, 15-21 points as moderate insomnia, and 22-28 points as severe insomnia.

IES-R is one of the most commonly used measurement tools in studies evaluating the mental health of health professionals during viral epidemic periods. In our study, it was decided to use IES-R as a measurement tool, and considering the relationship of PTSD with sleep, it was preferred to use it together with the ISI scale (17).

Statistical Analysis: Data were analyzed using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA), and presented as mean, standard deviation, median, minimum, maximum, percentage, and frequencies. Verilerin normal dağılıma uygunluğu Kolmogorov Smirnov testi ile kontrol edildi ve normal dağıldığı görüldü. Comparisons between categorical variables were performed with the Chi-Square test. In multivariate analysis, predictive risk factors between groups were examined by logistic regression analysis using possible risk factors identified in univariate analyzes. Adjusted odds ratios (ORs) and 95% confidence intervals (CI) were calculated. The test reliability was estimated using Cronbach α. A p-value of <0.05 was considered statistically significant.

RESULTS

Participants' Sociodemographic Characteristics and Responses Concerning COVID-19: The mean age of the participants was 20.7±1.6 years. Sociodemographic results are presented in Table 1.

Table 1. Sociodemographic characteristics of the participants

Variable		n	%
Sex	Female	393	54.4
	Male	329	45.6
Study year	1st grade	159	22
	2nd grade	278	38.5
	3rd grade	285	39.5
Residency place	At home (with family)	686	95
	At a student housing (with friends)	19	2.6
	At a student housing (alone)	7	1,0
	Dormitory	10	1.4
What is your level of knowledge about COVID-19?	Little	37	5.1
	Medium	249	34.5
	Enough	404	56
	Very well	32	4.4
Have you had COVID-19?	Yes	2	0.003
	No	722	99.7
Have any of your family members had COVID-19?	Yes	128	17.7
	No	594	82.3
What is your level of anxiety about the infection of your relatives with COVID-19?	None	13	1.8
	Little	131	18.1
	Middle	275	38.1
	High	303	42
What is your level of anxiety about infecting yourself with COVID-19?	Little	56	7.8
	Moderate	306	42.4
	Severe	227	31.4
	Extremely severe	133	18.4
What do you think about online learning?	Bad	277	38.4
	Middle	279	38.6
	Good	166	23
With which device do you attend the online learning sessions? †	I can't connect	5	0.7
	Smartphone	454	62.9
	PC	455	63
	Tablet	36	5
Is your internet quota limited?	Yes	244	33.8
	No	478	66.2
Has your daily screen time increased during the pandemic?	Yes	683	94.6
	No	39	5.4
What is your daily screen time during the pandemic? (on TV, smartphone, PC, tablet)	Less than 1 hour	9	1.2
	1-5 hours	233	32.2
	5-10 hours	415	57.4
	More than 10 hours	65	9
What is your level of anxiety about the interruption of your education?	None	51	7.1
	Little	105	14.5
	Middle	222	30.7
	High	344	47.7
What is your mostly-used source of information about COVID-19? †	TV	549	76
	Internet	584	80.9
	Social media	536	74.2
	Website of the ministry of health	280	36
	WHO's website	137	19

† multiple options selected

Opinions about Online Learning during the Pandemic: While 59.6% of the students (n=430) were happy with the online learning, 553 (76.3%) preferred the on-site educational environment in their school to online lectures. Students' perceptions about online learning are presented in Table 2.

Prevalence of Post-traumatic Stress Disorder (PTSD) and Insomnia: The mean IES-R score of the students was 24.5±15.1 (0-88), and the mean ISI score was 10.4±5.5 (0-28). The PTSD and insomnia prevalence was 25.1% and 23.6% respectively (Figure 1). No significant correlation was found between insomnia and PTSD (p=0.819).

Table 2. Students' perceptions about online learning

Perceptions	Agree n (%)	Disagree n (%)
I prefer OL to face-to-face lessons.	247 (34.2)	475 (65.8)
I am satisfied with OL.	430 (59.6)	292 (40.4)
I believe DE will be improved gradually.	531 (73.5)	191 (26.5)
OL must be interactive.	411 (56.9)	311 (43.1)
After the pandemic, some of the courses should continue as OL.	348 (48.2)	374 (51.8)
I'm happy with the learning environment in OL.	383 (53)	339 (47)
I prefer the educational environment in my school to OL.	551 (76.3)	171 (23.7)
I have internet access problems during OL.	316 (43.8)	406 (56.2)
I'm worried about what the exams are going to be like.	699 (96.8)	23 (3.2)
I'm worried that my practical learning will be incomplete.	647 (89.6)	75 (10.4)
I think my education will be incomplete due to OL.	599 (83)	123 (17)

OL: Online learning

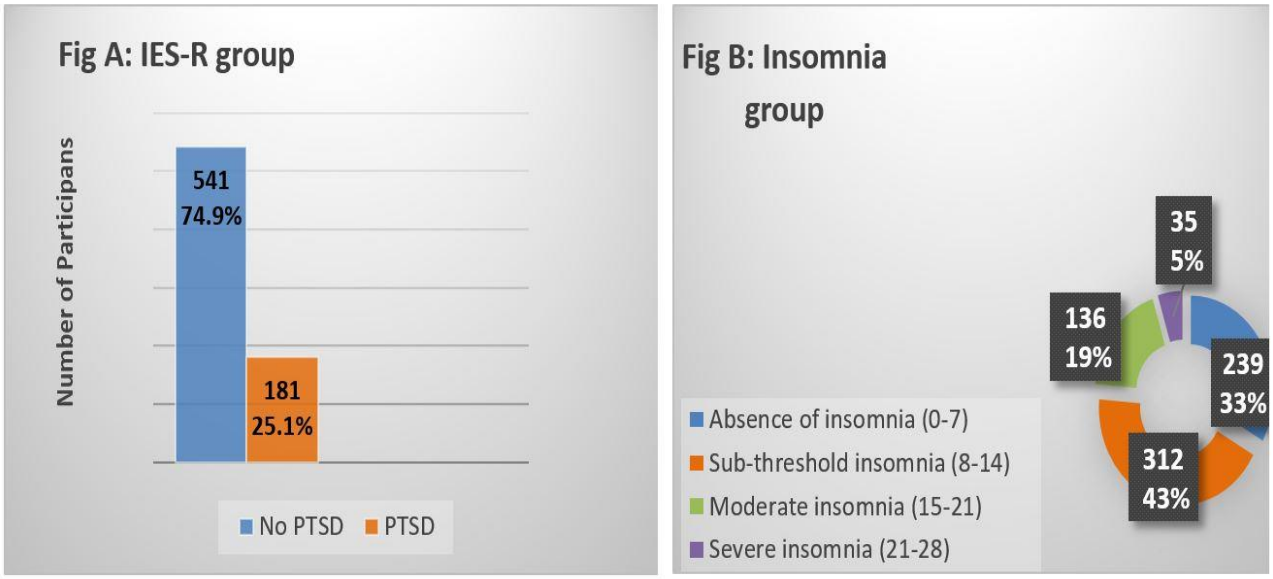

Figure 1. A) PTSD symptom prevalence, B) Insomnia symptom prevalence

The Relationship of PTSD and Insomnia with other Variables: PTSD was significantly higher in women compared to men (p=0.048), in those with acquaintances with COVID-19 compared to those without (p<0.001), in those who had a fear of having COVID-19 in their relatives compared to those did not have such fear (p<0.001), those following COVID-19-related news on social media compared to those who did not follow such news (p=0.004), those who had a high level of anxiety about the interruption of education compared to those who had less anxiety (p<0.001) (Table 3).

PTSD scores were significantly higher among participants with internet access and quota problems (p<0.001 and p=0.007, respectively), those with a bad perception of online learning (p<0.007), and those who were not satisfied with online learning (p=0.001) (Table 4). Both PTSD (p<0.001) and insomnia (p=0.013) were significantly higher in those with a high fear of contagion with COVID-19 among relatives.

PTSD Probabilities According to Selected Demographic Characteristics: A logistic regression model was created with variables, and the results are summarized in Table 5.

Table 3. The association of PTSD and insomnia with sociodemographic characteristics

		IES-R Group						ISI Group					
		<33		≥ 33				Normal		Insomnia			
		n	%	n	%	χ^2	p	n	%	n	%	χ^2	p
Sex	Men	258	47.7	71	39.2	3.91	**0.048**	251	45.6	78	45.6	0.000	0.989
	Women	283	52.3	110	60.8			300	54.4	93	54.4		
Study year	Phase 1	118	21.8	41	22.7	1.35	0.507	114	20.7	45	26.3	2.710	0.258
	Phase 2	203	37.5	75	41.4			213	38.7	65	38.0		
	Phase 3	220	40.7	65	35.9			224	40.7	61	35.7		
Do you have any acquaintances with COVID-19	Yes	80	14.8	48	26.5	12.79	**<0.001**	98	17.8	30	17.5	0.005	0.942
	No	461	85.2	133	73.5			453	82.2	141	82.5		
What is your level of anxiety about your relatives (mother. father. sibling. close relative) being infected with COVID-19?	None	11	2.0	2	1.1	34.46	**<0.001**	9	1.6	4	2.3	6.170	**0.013**
	Little	110	20.3	21	11.6			93	16.9	38	22.2		
	Medium	233	43.1	42	23.2			204	37.0	71	41.5		
	High	187	34.6	116	64.1			245	44.5	58	33.9		
What is your level of anxiety about yourself being infected with COVID 19?	None	0	0.0	0	0.0	1.35	0.716	0	0.0	0	0.0	3.675	0.299
	Little	39	7.2	17	9.4			43	7.8	13	7.6		
	Medium	227	42.0	79	43.6			225	40.8	81	47.4		
	High	174	32.2	53	29.3			174	31.6	53	31.0		
Social media	Yes	387	71.5	149	82.3	8.25	**0.004**	413	75.0	123	71.9	0.624	0.429
	No	154	28.5	32	17.7			138	25.0	48	28.1		
WHO's web site	Yes	100	18.5	37	20.4	0.33	0.561	116	21.1	21	12.3	6.531	**0.011**
	No	441	81.5	144	79.6			435	78.9	150	87.7		
How would you describe your level of knowledge about COVID-19?	Very low	33	6.1	4	2.2	5.73	0.126	34	6.2	3	1.8	11.714	**0.008**
	Medium	188	34.8	61	33.7			200	36.3	49	28.7		
	Sufficient	294	54.3	110	60.8			291	52.8	113	66.1		
	Very good	26	4.8	6	3.3			26	4.7	6	3.5		
What is your level of anxiety about the interruption of your education?	None	44	8.1	7	3.9	42.14	**<0.001**	42	7.6	9	5.3	4.309	0.366
	Low	80	14.8	25	13.8			75	13.6	30	17.5		
	Medium	186	34.4	36	19.9			164	29.8	58	33.9		
	High	142	26.2	44	24.3			148	26.9	38	22.2		
	Very high	89	16.5	69	38.1			122	22.1	36	21.1		

Table 4. Relationships of PTSD and insomnia with views on online learning

		IES-R Group						ISI Group					
		<33		≥ 33				Normal		Insomnia			
		n	%	n	%	χ^2	p	n	%	n	%	χ^2	p
What are your thoughts about OL ?	Bad	184	34.0	93	51.4	17.34	**<0.001**	220	39.9	57	33.3	9.398	**0.009**
	Medium	223	41.2	56	30.9			219	39.7	60	35.1		
	Good	134	24.8	32	17.7			112	20.3	54	31.6		
Does your internet have a limited quota	Yes	168	31.1	76	42.0	7.24	**0.007**	182	33.0	62	36.3	0.607	0.436
	No	373	68.9	105	58.0			369	67.0	109	63.7		
I prefer OL to face-to-face lessons.	I agree	186	34.4	61	33.7	0.02	0.868	177	32.1	70	40.9	4.503	**0.034**
	I disagree	355	65.6	120	66.3			374	67.9	101	59.1		
I am satisfied with OL.	I agree	341	63.0	89	49.2	10.81	**0.001**	327	59.3	103	60.2	0.043	0.836
	I disagree	200	37.0	92	50.8			224	40.7	68	39.8		
I believe OL will be improved gradually.	I agree	411	76.0	120	66.3	6.52	**0.011**	409	74.2	122	71.3	0.558	0.455
	I disagree	130	24.0	61	33.7			142	25.8	49	28.7		
OL must be interactive.	I agree	307	56.7	104	57.5	0.02	0.867	324	58.8	87	50.9	3.343	0.068
	I disagree	234	43.3	77	42.5			227	41.2	84	49.1		
After the pandemic, some of the courses should continue as OL.	I agree	263	48.6	85	47.0	0.14	0.700	254	46.1	94	55.0	4.115	**0.043**
	I disagree	278	51.4	96	53.0			297	53.9	77	45.0		
I'm happy with the learning environment in OL.	I agree	308	56.9	75	41.4	13.07	**<0.001**	287	52.1	96	56.1	0.861	0.354
	I disagree	233	43.1	106	58.6			264	47.9	75	43.9		
I prefer the educational environment in my school to OL.	I agree	422	78.0	129	71.3	3.402	0.065	433	78.6	118	69.0	6.624	**0.010**
	I disagree	119	22.0	52	28.7			118	21.4	53	31.0		
I have internet access problems during OL.	I agree	215	39.7	101	55.8	14.213	**<0.001**	251	45.6	65	38.0	3.016	0.082
	I disagree	326	60.3	80	44.2			300	54.4	106	62.0		
I think my education will be incomplete due to OL.	I agree	441	81.5	158	87.3	3.203	0.074	478	86.8	121	70.8	23.611	**<0.001**
	I disagree	100	18.5	23	12.7			73	13.2	50	29.2		

OL Online learning

Table 5. Multivariate analysis of the effects of variables on PTSD

	B	SE	p	OR	95% CI for EXP(B)	
					Lower	Upper
Sex	0.398	0.192	0.038	1.489	1.023	2.167
Do you have any acquaintances with COVID-19	-0.648	0.221	0.003	0.523	0.339	0.807
What is your level of anxiety about your relatives being infected with COVID-19?	0.640	0.130	<0.001	1.896	1.471	2.445
What is your level of anxiety about the interruption of your education?	0.270	0.084	0.001	1.310	1.111	1.543
I am not satisfied with distance lessons.	0.541	0.191	0.005	1.717	1.180	2.498
I have internet access problems during OL	-0.412	0.185	0.026	0.662	0.461	0.951
Constant	-3.512	0.825	<0.001	0.030		

SE: standard error, CI: confidence interval, OR: odds ratio

The probability of PTSD was higher in those who had more fear of COVID-19 transmission to their relatives than in students who had little or no fear (OR=0.523, 95% CI=0.339-0.807; p=0.003). The probability of PTSD was higher in students who followed the news about COVID-19 from social media than those who followed it from other sources (OR=1.489, 95% CI=1.02-2.16; p=0.038). The probability of PTSD in students who are dissatisfied with online learning is higher than that of those who are satisfied (OR=1.717.95% CI=1.180-2.498; p=0.001), and the probability of PTSD in students who had internet problems in online learning was higher than the probability of PTSD in those who did not (OR=0.662, 95% CI=0.461-0.951; p<0.001). The probability of PTSD was higher in students who were worried that their education would be incomplete than those who were not worried (OR=1.310, 95% CI=1.111-1.543; p=0.001).

DISCUSSION

In this study it is found that the medical students were seriously affected psychologically by the COVID-19 pandemic; one out of four students had PTSD and or insomnia.

In a study conducted in Italy at the peak of the epidemic, PTSD was found in nearly half of the healthcare workers and 29.5% of the general population, while insomnia was seen in 8% of the healthcare workers (24, 25). In a multicenter study conducted with healthcare professionals in China, the prevalence of PTSD was 9.1% (26), which was 16.3% in university students (27). Looking at these studies, the PTSD rate in the study in China is lower than our study, and it is much higher in Italy. The frequency of insomnia reported in both studies is much lower than our results. Factors such as the stage of the epidemic, the study group, sociocultural differences, and the number of cases may have been effective in these differences.

We found a higher probability of PTSD in women. The findings in the literature on this issue are contradictory. A study conducted in Italy reported higher rates in women (28), while a study conducted in China found higher rates in men (29). Sociocultural and regional characteristics may have been effective in these differences.

In current study, we found insomnia in one-fourth of the students. Insomnia was more common in students who were concerned about the negative impact on education. In a study conducted with healthcare professionals in Wuhan, sleep disorders were found in 38% of the participants, and contact with COVID-19 patients was determined to be a risk factor for sleep disorders (30). In another study, moderate insomnia was found in 61.6% and several insomnia in 26.6% of frontline workers in a pandemic hospital (31). In a multicenter study conducted with healthcare professionals in China, the rate of insomnia was 36.1% (20). The studies mentioned above, which have high rates of insomnia, have been conducted with health professionals working in the hospital and on the front line. In the current study, insomnia rates are lower. This may ultimately be effective if the students are in the preclinical stage and do not participate in on-patient practices.

It was reported that fear of being infected, having an infected relative, and following the relevant news on social media were risk factors for insomnia (32). In the current study, insomnia was more common in students who had a fear of transmitting the disease to their relatives. In addition, insomnia was significantly higher in students who thought that online learning was bad, who preferred the face-to-face education environment to the online learning environment, and who thought that their education would be incomplete due to online learning.

In some studies, it has been reported that insomnia is more common in women (32, 33), but this has not been confirmed in our study.

It is found that about half of the students (49.8%) were concerned about getting themselves infected with COVID-19. In a study conducted with interns, the anxiety of transmitting COVID-19 to students was higher (64.7%) than our finding (33). The fact that the study mentioned above was

conducted at the beginning of the pandemic and that the interns were working face-to-face with the patients may have been effective in the high contagion concerns.

The students' anxiety about the contagion of their relatives was about twice as much as their anxiety of infecting themselves, and PTSD was significantly higher in students who had a high level of contagion anxiety. We did not find any studies investigating the relationship between fear of contracting COVID-19 to relatives and the risk of PTSD. However, the survey by Safa et al. reported that individuals with severe stress about acquiring COVID-19 had higher anxiety and depressive symptoms (34). Another study reported that PTSD is more common in students who had a relative with COVID-19 or lost a relative due to COVID-19 (27). In our study, having a relative infected with COVID-19 was a risk factor for PTSD. Studies have reported similar results (35, 36). These results show that the relatives of the students experience more stress for their health.

With the closure of schools during the pandemic, education moved to online platforms. Students who were at home during this period tended to seek information about the disease from various sources. Studies show that students frequently use social media as a source of information (35, 37, 38). Social media is also a socialization tool for young people. However, there may be false or sensational information, which may spread without being verified for its correctness (39). We found significantly higher PTSD in students who followed COVID-19 news on social media. Studies have reported higher levels of depression and anxiety in individuals who followed COVID-19 news on social media (40, 41). It may be beneficial to provide students with timely, up-to-date information from their teaching institutions and direct them to suitable information sources for self-directed learning (42). The transfer of accurate and up-to-date information to students by educational institutions will allow them to obtain information from the correct and first source, prevent stress caused by obtaining unlimited and fast information, the accuracy of which has not been checked on social media.

Online learning is very valuable because it ensures the continuation of education during the pandemic process. However, although it is extremely effective for theoretical trainings, it is difficult to say that it is equally successful for practical trainings and applications. As a matter of fact, we have seen that all students had severe concerns about the interruption of their practical education. Planning compensation programs for practical training after the pandemic process and informing students about the issue may reduce their concerns.

Six out of ten students were satisfied with OL, and two-thirds believed that OL would gradually be improved. However, the majority of the students preferred the educational environment at their school to online education. In a study conducted in the UK, students also stated that they prefer a face-to-face educational environment (43).

Online learning conducted during the pandemic process has been an experience for students that they have not been used to until that day. Factors such as the fact that educators, like students, are not experienced enough in OL, and practical training cannot be done remotely have caused stress that their education will be incomplete in students.

Nearly half of the students participating in the study had internet connection problems, and one-third had quota problems. When it is considered that most of the education was done online, factors such as internet access problems, connection problems, quota problems, and/or low internet speed cause problems, such as not being able to connect to the courses, image freezing, audio interruptions, as well as causing inequality of opportunity among students and reducing the efficiency of education.

In our study, there was a significant predictive effect of educational anxiety on PTSD and insomnia. PTSD is raised comprehensively in students who are not satisfied with OL and prefer OL environment at school. It was found that students who are dissatisfied with OL, who prefer face-to-face education, who prefer the educational environment at school to OL, who think that education will remain sour, have a high understanding of alertness.

In online learning, an internet connection is required for students to attend classes. Factors such as lack of access to the Internet, quota problem, connection speed directly affect students' course attendance and the decision they will make from the course. For example, a slow binding can cause freezes, interruptions in the image and sound. With the quota exam, students may not be able to attend the course. Our study results show that the understanding of PTSD is significantly higher in students with internet access and quota problems. In addition, the logistic regression analysis shows that the probability of PTSD is higher in students with internet connection problems. In order to avoid these questions, improving the infrastructure of internet connection, increasing internet speed, solving quota problems, applying importance such as free or affordable internet service to students can reduce educational concerns.

This study was carried out in the second wave of the epidemic in Turkey. Online learning of medical students reflects their views on the state of PTSD and insomnia. Students are experiencing the psychological effects of the pandemic, sleeping at a high rate, and showing signs of PTSD. Students are shifting to the seriousness that their education will remain sour. Strategies should be developed to

support students and increase their endurance. Online information, counseling and intervention activities can contribute to their mental well-being.

In this process, it is very important to ensure that students get the right information and correct their incorrect information. It is recommended to provide social support, check the correctness of information sources and provide easily accessible psychological support.

Limitations: The study has some limitations. First of all, this is a cross-sectional study. It was conducted with preclinical students of a single medical faculty. Therefore, the results cannot be generalized to all medical students. Second, the data are based on students' self-evaluations. The participants' memory is involved in the answers, and it is not possible to avoid prejudice. Finally, as the study was conducted with an online questionnaire, there is also the possibility of selection bias. The inability to reach students who did not have a device or internet and did not use social media may have impacted the results.

CONCLUSION

This study shows that medical students are experiencing the psychological effects of the pandemic and are seriously concerned that their education is incomplete. One in four students experience PTSD or insomnia. Students are more worried about their relatives getting infected than if they were infected themselves. Medical students are at high risk of PTSD and insomnia.

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RESEARCH ARTICLE

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The Clinical Correlations of Fatigue in Patients with Sarcoidosis

ABSTRACT

Objective: Fatigue is considered a frequent and characteristic feature of sarcoidosis. This study was designed to determine the prevalence of fatigue in patients with sarcoidosis and to determine its potential clinical correlations in relation to symptom severity.

Methods: A total of 56 sarcoidosis patients were included. Data on patient demographics, anthropometrics, disease characteristics, pulmonary function tests, 6-min walking distance (6MWD), blood biochemistry and hemogram findings were retrieved from hospital records. Psychometric instruments involved fatigue assessment scale (FAS), Beck Depression Inventory (BDI) and Short Form-36 (SF-36) for health-related QOL (HRQOL).

Results: Mean±SD patient age was 50.9±11.9 years. Of 56 patients, 44 were females and 12 were males. When compared to FAS score <22 and FAS score ≥22-34 subgroups, FAS score ≥35 (severe fatigue) subgroup was associated with significantly higher patient age and significantly lower SF-36 physical health scores. Total FAS scores were correlated positively with age (r=0.349, p=0.008) and BDI scores (r=0.515, p<0.001), while negatively with MIP (r=-0.321, p=0.019) and SF-36 physical health (r=-0.402, p=0.003) and mental health (r=-0.351, p=0.009) scores. BDI score (OR 1.146, 95% CI: 1.020 to 1.288, p=0.021) was determined to be the single independent predictor of increased likelihood of a patient with sarcoidosis to have FAS score ≥22.

Conclusions: Our findings emphasize that deterioration in respiratory functions may contribute to development of fatigue among sarcoidosis patients, and besides the fatigue, depressive symptoms and anxiety should also be an integral part of the multidisciplinary management of sarcoidosis patients.

Keywords: Fatigue Assessment Scale (FAS), Fatigue, Health Quality, Sarcoidosis.

Sarkoidoz Hastalarında Yorgunluğu Etkileyen Klinik Etkenler

ÖZET

Amaç: Yorgunluk, sarkoidozun sık ve karakteristik bir özelliği olarak kabul edilir. Bu çalışma, sarkoidozlu hastalarda yorgunluk prevalansını belirlemek ve semptom şiddeti ile ilişkili potansiyel klinik korelasyonlarını belirlemek için tasarlanmıştır.

Gereç ve Yöntem: Toplam 56 sarkoidoz hastası dahil edildi. Hastane kayıtlarından hasta demografisi, antropometri, hastalık özellikleri, solunum fonksiyon testleri, 6 dakikalık yürüme mesafesi (6DYM), kan biyokimyası ve hemogram bulgularına ilişkin veriler elde edildi. Psikometrik araçlar, sağlıkla ilgili yaşam kalitesi (HRQOL) için yorgunluk değerlendirme ölçeği (YDÖ), Beck Depresyon Ölçeği (BDÖ) ve Kısa Form-36 (SF-36) kullanıldı.

Bulgular: Ortalama ± SS hasta yaşı 50.9 ± 11.9 yıldı. 56 hastanın 44'ü kadın, 12'si erkekti. YDÖ skoru <22 ve YDÖ skoru ≥22-34 alt grupları ile karşılaştırıldığında, YDÖ skoru ≥35 (şiddetli yorgunluk) alt grubu, daha yüksek hasta yaşı (p = 0.037) ve anlamlı olarak daha düşük SF-36 fiziksel sağlık skorları (p = 0.029) ile anlamlı bulundu. Toplam YDÖ skorları yaş (r = 0.349, p = 0.008) ve BDÖ skorları (r = 0.515, p <0.001) ile pozitif korelasyon gösteriyor iken; MIP (r = -0.321, p = 0.019) ve SF-36 fiziksel sağlık (r = -0.402, p = 0.003) ve mental sağlık(r = -0.351, p = 0.009) puanları sağlık ile negatif korelasyon gösteriyordu. BDÖ skorunun (OR 1.146,% 95 CI: 1.020 - 1.288, p = 0.021), sarkoidoz hastalarının YDÖ skorunun ≥22 olması olasılığının artmasının tek bağımsız prediktörü olduğu belirlendi.

Sonuç: Bulgularımız, solunum fonksiyonlarındaki bozulmanın sarkoidoz hastalarında yorgunluğun gelişimine katkıda bulunabileceğini ve yorgunluğun yanı sıra depresif belirtiler ve anksiyetenin sarkoidoz hastalarının multidisipliner yönetiminin ayrılmaz bir parçası olması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Yorgunluk Değerlendirme Ölçeği (YDÖ), Sarkoidoz, Yaşam Kalitesi, Yorgunluk

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder that may affect any organ system, while it affects lungs in more than 90% of cases (1,2). In the clinical course of sarcoidosis, there exists not only the organ-specific involvement and related dysfunction but also rather nonspecific symptoms (3). Hence, sarcoidosis patients may suffer from a wide spectrum of nonspecific symptoms, such as fatigue, weight loss, fever, night sweats, arthralgia, muscle pain, exercise limitation and cognitive failure (4,5).

Fatigue is considered a frequent and characteristic feature of sarcoidosis, as associated with significant negative impact on the patients' quality of life (QOL) depending on the severity that ranges from mild to persistent and disabling symptoms (6,7). The exact etiology of fatigue in patients with sarcoidosis remains largely unknown, while is considered to be multifactorial with potential contribution of comorbidities, treatments and psychological factors in addition to chronic systemic inflammation (6,8). Amongst the factors suggested to be associated with occurrence of fatigue in active disease are systemic inflammation, muscle involvement, extra-pulmonary locations, comorbidities, pulmonary hypertension, impaired lung function, steroids and other drugs used for the treatment of sarcoidosis and psychological factors (6).

Many patients continue to experience fatigue despite receiving an adequate sarcoidosis treatment (8). In addition, despite a comprehensive search for treatable clinical causes of fatigue, complaints of fatigue are not correlated with clinical parameters of disease activity in most patients (8).

This study was therefore designed to determine the prevalence of fatigue in patients with sarcoidosis and to determine its potential clinical correlations in relation to symptom severity.

MATERIAL AND METHODS

Study Population: A total of 56 sarcoidosis outpatients being followed up at a tertiary-care center were included in this study.

The permission was obtained from our institutional ethics committee for the use of patient data for publication purposes (Date of Approval: 18.03.2019; Reference number/Protocol No:2019/73).

Assessments: Data on patient demographics (age, gender), anthropometrics [body mass index (BMI, kg/m^2), waist circumference (cm) and hip circumference (cm)], disease characteristics (duration of disease, radiographic stage, treatments), pulmonary function tests [% predicted values for forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), DLCO/VA (transfer coefficient), maximal inspiratory pressure (MIP) and total lung capacity (TLC)], 6-min walking distance (6MWD), blood biochemistry and hemogram findings were retrieved from hospital records. Psychometric instruments involved fatigue assessment scale (FAS), Beck Depression Inventory (BDI) and Short Form-36 (SF-36) for health-related QOL (HRQOL).

Fatigue Assessment Scale: The FAS is a 10-item validated and reliable scale, developed by De Vries et al. being used to assess fatigue in sarcoidosis patients. Each item is scored based on a 5-point Likert scale ranging from "never" to "always," and the total score range is 10–50. Scores <22 indicate absence of fatigue, while scores between 22 and 34 indicate mild-to-moderate fatigue, and scores ≥ 35 indicate severe fatigue (7,9). The Turkish version of the questionnaire used was obtained from https://wasog.org/dynamic/media/78/documents/Questionairres/fas_tur_anon.html.

Beck Depression Inventory: BDI is a 21-item self-reporting questionnaire for evaluating the level and change in severity of depression based on physical, emotional, cognitive and motivational symptoms. Each item is scored on a 4-point scale from 0 (symptom absent) to 3 (severe symptoms), while the total score achieved by adding the highest ratings for all 21 items ranges from 0 to 63 with higher scores indicating greater symptom severity (10).

Statistical Analysis: Statistical analysis was made using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Kruskal-Wallis H test was used to compare the continuous variables between FAS subgroups. Correlation of FAS scores with BDS, SF-36 physical and mental health scores and pulmonary function test parameters were analyzed via Pearson correlation analysis. Binary logistic regression analysis was performed to determine factors predicting presence of FAS scores ≥22 in sarcoidosis patients. Data were expressed as mean± standard deviation (SD), median (interquartile range, IQR) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics: Mean±SD patient age was 50.9±11.9 years. Of 56 patients, 44 (79%) were females and 12 (21%) were males. Overall, stage 1, 2 and 3 sarcoidosis was evident in 6 (10.7%), 46 (82.1%) and 4 (7.1%) patients, respectively. Considering steroid treatment, 32 patients were treatment-native, 18 patients had previous treatment and 6 patients were under steroid therapy (Table 1).

Considering pulmonary function tests, mean±SD % predicted values were 101.1±14.8 for FVC, 94.3±16.8 for FEV1, 91.6±21.6 for DLCO/VA, -79.6±24.4 for MIP and 91.5±19.4 for TLC, while mean±SD 6MWD was 405.2±85.5 m (Table 1).

FAS assessment revealed absence of fatigue (FAS score <22) in 21.4% of patients, while mild-to-moderate fatigue (FAS score ≥22-34) was noted in 62.5% of patients and severe fatigue (FAS score ≥35) in 16.1% of patients (Table 1).

Nearly half of the patients were in the mild depression group according BDI scores, while mean±SD SF-36 scores were 64.1±21.9 for the physical health domain and 63.0±23.2 for the mental health domain (Table 1).

Table 1. Demographic and clinical characteristics (n=56)

Patients characteristics	
Gender (Male/Female)	44/12
Age (year), mean±SD	50.9 ± 11.9
BMI (kg/m^2), mean±SD	31.3 ± 4.8
Disease characteristics	mean±SD
Duration of disease (year)	4.4 ± 4.2
Radiographic stage	n(%)
1	6 (10.7)
2	46 (82.1)
3	4 (7.1)
Respiratory parameters (% predicted value)	**mean±SD**
FVC	101.1 ± 14.8
FEV1	94.3 ± 16.8
DLCO/VA	91.6 ± 21.6
MIP	-79.6 ± 24.4
TLC	91.5 ± 19.4
6MWD	405.2 ± 85.5
Fatigue assessment (FAS scores)	**n(%)**
FAS score <22	12 (21.4)
FAS score 22-34	35 (62.5)
FAS score ≥35	9 (16.1)
Beck Depression Inventory	**n(%)**
No depression	16 (28.6)
Mildly depressed	26 (46.4)
Moderately depressed	11 (19.6)
Severely depressed	3 (5.4)
SF-36 scores	**mean±SD**
Physical health	64.1 ± 21.9
Mental health	63.0 ± 23.2
Steroid use	**n(%)**
Never	32 (57.1)
Previously used	18 (32.1)
Still using	6 (10.7)

BMI: Body mass index, FVC: Forced vital capacity; FEV1: Forced expiratory volume at 1 sec; DLCO/VA: Transfer coefficient; MIP: Maximal inspiratory pressure; TLC: Total lung capacity; 6MWD: 6-min walk distance; FAS: Fatigue assessment scale; SF-36: 36-item short form survey

Study Parameters with respect to FAS Subgroups: When compared to FAS score <22 and FAS score ≥22-34 subgroups, FAS score ≥35 (severe fatigue) subgroup was associated with significantly higher patient age (median 60.0 vs. 53.5 and 53.0 years, respectively, p=0.037) and significantly lower SF-36 physical health scores (median 51.8 vs. 83.5 and 70.0, respectively, p=0.029) (Table 2). A non-significant tendency for higher BDI scores along with lower SF-36 mental health scores and lower MIP and 6MWD values were noted in FAS score ≥35 subgroup as compared with other FAS subgroups (Table 2).

Correlation of Total FAS Score with Study Parameters: Total FAS scores were correlated positively with age (r=0.349, p=0.008) and BDI scores (r=0.515, p<0.001), while negatively with MIP (r=-0.321, p=0.019) and SF-36 physical health (r=-0.402, p=0.003) and mental health (r=-0.351, p=0.009) scores. No significant difference was noted in pulmonary function test parameters between FAS sub-groups (Table 3).

Multivariate Analysis of Risk Factors Predicting presence of FAS scores ≥22: BDI score (OR 1.146, 95% CI: 1.020 to 1.288, p=0.021) was determined to be the single independent predictor of increased likelihood of a patient with sarcoidosis to have FAS score ≥22.

Table 2. Physical and clinical characteristics according to FAS subgroups

	FAS subgroups			
Variables	**FAS <22 (n=12)**	**FAS ≥22-34 (n=35)**	**FAS ≥35 (n=9)**	**p value**
Age (year)	53.5 (49.2 – 57.0)	53.0 (37.0 – 56.0)	60.0 (56.0 – 66.0)	0.037
Body mass index (kg/m^2)	34.0 (30.0 - 36.5)	30.0 (27.0 – 35.0)	33.0 (29.0 – 35.2)	0.093
Waist circumference (cm)	107.5 (90.7-115.7)	101.0 (94.0-108.0)	98.0 (94.2-115.0)	0.656
Hip circumference (cm)	112.5 (100.5-121.7)	106.0(102.0-117.0)	107.5(101.2-121.2)	0.751
Beck depression inventory score	10.5 (2.0 – 15.2)	12.5 (9.0 – 19.2)	19.0 (13.0 -30.5)	0.054
SF-36 physical health score	83.5 (57.7 – 89.2)	70.0 (51.0 – 82.8)	51.8 (38.6 – 55.1)	**0.029**
SF-36 mental health score	82.3 (55.1 – 92.8)	69.7 (43.8 – 82.1)	42.7 (38.3 – 76.7)	0.506
6-min walk distance (m)	426.5 (378.7-503.0)	416.5 (333.0-471.0)	385.0 (355.0-420.0)	0.254
FVC (% predicted)	105.5 (98.0 -.114.7)	101.0 (88.0 - 107.0)	98.0 (93.5 – 111.5)	0.352
FEV1 (%predicted)	105.5 (94.0 -108.0)	90.0 (81.0 – 104.0)	93.0 (83.0 – 102.0)	0.119
DLCO/VA(%predicted)	99.5 (84.0 – 106.7)	91.0 (86.2 – 102.2)	96.5 (32.7 – 110.7)	0.505
MIP (%predicted)	87.0 (73.0 – 94.5)	83.5 (60.5 – 101.2)	68.0 (36.0 – 75.0)	0.135
TLC (%predicted)	92.0 (77.0 – 99.5)	86.0 (78.5 – 99.0)	100.0 (85.5 – 115.0)	0.305

Data are shown as median (25-75% quartile).

SF-36: Short form -36; FVC: Forced vital capacity; FEV1: Forced expiratory volume at 1 sec; DLCO/VA: transfer coefficient; MIP: Maximal inspiratory pressure; TLC: Total lung capacity

Table 3. Correlation of FAS total score with study variables

Variables	FAS total score	
	r	p
Age (year)	0.349	**0.008**
Body mass index (kg/m^2)	0.020	0.883
6-min walk distance (m)	-0.268	0.058
FVC (%predicted)	-0.149	0.273
FEV1 (%predicted)	-0.242	0.072
DLCO/VA(%predicted)	-0.230	0.108
MIP (%predicted)	-0.321	**0.019**
TLC (%predicted)	0.127	0.354
Beck depression inventory score	0.515	<0.001
SF-36 physical health score	-0.402	**0.003**
SF-36 mental health score	-0.351	**0.009**

SF-36: Short form -36; FVC: Forced vital capacity; FEV1: Forced expiratory volume at 1 sec; DLCO/VA: transfer coefficient; MIP: Maximal inspiratory pressure; TLC: Total lung capacity; r:correlation coefficient
Pearson correlation analysis

DISCUSSION

Our findings revealed significantly lower SF-36 physical health scores along with tendency for higher BDI scores, lower SF-36 mental health scores and lower MIP and 6MWD values in patients with severe fatigue when compared to those with mild-to-moderate fatigue or without fatigue. Logistic regression analysis revealed significantly higher likelihood of having fatigue among sarcoidosis patients with increase in BDI scores (OR, 1.146).

The findings in the current study indicated high prevalence of fatigue (78.6% overall, mild-to-moderate in 62.5% and severe in 16.1%) among sarcoidosis patients. This seems consistent with data from a past study in 145 Croatian sarcoidosis patients, indicated mild-to-moderate fatigue in 42% of patients and severe fatigue (FAS scores 35-50) in 15% of patients with lack of fatigue (FAS scores 10–21) in 43% of sarcoidosis patients (6).

There are few reports pointing out the possible link between fatigue and depression (11). Goracci et al. (12) indicated high rates of psychiatric comorbidity in sarcoidosis patients and its potential contribution to a poorer quality of life. De Klejn et al. (13) reported anxiety and depressive symptoms to be significant predictors of high fatigue scores and thus the likelihood of fatigue to be related to co-morbid depression and anxiety in patients suffering from active sarcoidosis. However, the impact of underlying depression on fatigue has not been studied in patients with sarcoidosis in clinical remission (11). In a study by Chang et al. (14) among 176 sarcoidosis patients, the rate of depression was reported to be 60%. In our study, depression was noted in 71.4% according to BDI score (≥9), while BDI score was determined to be a significant independent predictor of having FAS scores ≥22.

There are studies on the relationship between sarcoidosis and QOL (15,16). The satisfaction with life is considered an outcome with special relevance among patients with a potentially chronic disease like sarcoidosis, as it is affected directly and indirectly by health and disease, or HRQOL (17). In a study by Cox et al. (18) in 111 sarcoidosis patients, assessment of QOL with St. George Respiratory Questionnaire (SGRQ) revealed a decrease in quality of life.

In another study among sarcoidosis patients by Michielsen et al. (7), authors indicated association of fatigue with all QOL domains and the likelihood of fatigue measured by the FAS to be a good indicator of QOL in sarcoidosis patients. In the current study, SF-36 physical health scores were significantly lower in patients with FAS scores ≥ 35 alongside a significant negative correlation of FAS scores with both mental and physical component scores of SF-36. Accordingly, our findings seems to indicate that the likelihood of poor QOL in patients with sarcoidosis to be due to fatigue-related symptoms.

Fatigue and general weakness may be the reason why patients with sarcoidosis frequently experience exercise intolerance, a symptom also noted frequently in other chronic inflammatory states, such as chronic fatigue syndrome (19-21). In a study by Baydur et al. the relation between plasma cytokine levels and fatigue in sarcoidosis patients was assessed by a multifactorial inventory instrument (22). Comparing the plasma cytokine concentrations before and immediately after cardiopulmonary exercise testing in sarcoidosis patients and control subjects, authors reported a relationship between fatigue and plasma IL-1b concentrations in sarcoidosis patients treated with immunomodulating drugs (22).

The association of fatigue with decreased muscle strength and exercise intolerance has consistently been reported by studies among sarcoidosis patients (11,23). In a study by Karadalli et al., 15 sarcoidosis patients who received inspiratory muscle training (IMT) for 6 weeks were compared with the control group and authors reported the association of IMT with improved functional and maximal exercise capacity and respiratory muscle strength and decreased severity of fatigue and dyspnea perception among patients in the early stages of sarcoidosis (24). Likewise, our findings revealed a negative correlation between FAS severity and MIP, emphasizing the likelihood of IMT training to decrease the FAS score and improve the QOL among the sarcoidosis patients.

Skeletal muscle involvement can occur in sarcoidosis, while myositis with significant elevation of the muscle enzymes in the blood stream is relatively rare. If respiratory muscles are involved, it can lead to respiratory failure (25,26). In a prospective study of 34 sarcoidosis patients with pulmonary disease, peak inspiratory muscle pressure (PImax) was reported to be significantly lower than the control group (27). Muscle strength

has been shown to affect the 6MWD (28). In a study by Baughman et al. in 142 sarcoidosis patients, measurement of 6MWD over a 6-week period revealed more than half of patients to have a 6MWD of less than 400m and 32 (22%) patients to walk less than 300 m, along with a correlation between FAS scores and 6MWD (29,30). Similarly, a negative correlation between FAS score and 6MWT was also noted in our study.

The most important limitation of the study is a relatively small sample size. Another limitation is the fact that the symptoms were self-reported, which could lead to bias. However, the burden of sarcoidosis is determined by the experience of the patients themselves. One of the limitations of our study is; it was not evaluated whether the patient's job, being married or having children, which would affect the quality of life of the patients.

In conclusion, our findings indicate fatigue to be a prevalent symptom in sarcoidosis. This emphasizes the need for developing a good questionnaire to assess fatigue in sarcoidosis patients given that no medical parameters are yet available to objectively assess the fatigue. FAS scores in our sarcoidosis patients showed a significant positive correlation with BDI and a strong negative correlation with MIP along with a negative but non-significant correlation with PFT. Accordingly, our findings emphasize that deterioration in respiratory functions may contribute to development of fatigue among sarcoidosis patients, and besides the fatigue, depressive symptoms and anxiety should also be an integral part of the multidisciplinary management of sarcoidosis patients.

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RESEARCH ARTICLE

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Retrospective Analysis of Methyl Alcohol Poisonings Admitted to the Emergency Department

ABSTRACT

Objective: Methyl alcohol poisoning remains a significant cause of mortality and morbidity. This poisoning is still one of the important reasons for admission to emergency services. We aimed to examine the admission complaints, laboratory findings, treatment methods, clinical outcomes and examine the factors affecting the mortality of patients diagnosed with methyl alcohol poisoning in the emergency department.

Methods: In this retrospective descriptive study, we analysed the patients who were considered to be diagnosed with methyl alcohol intoxication among those who came to our emergency department due to alcohol intoxication from June 1, 2018 to June 1, 2020.

Results: The study included 20 (4.86%) individuals with methyl alcohol poisoning among 411 people who presented to the emergency department due to ethyl and methyl alcohol intake and resulting effects. The mean age of the patients was 47.35±14.2 years and 85% (n=17/20) were male. Upon reviewing the patients' admission symptoms, 70% were observed to have visual problems, 60% complaints of vomiting, 45% shortness of breath, and 40% changes in consciousness. In the study, it was revealed that 18.2%(n=2/11) females and 81.8%(n=9/11) males died, and the mortality rate was calculated as 55%(n=11/20).

Conclusions: The presence of visual problems, hypotension, and coma in clinical findings, high anion gap metabolic acidosis, marked osmolar gap, an increase in lactate level, and hyperglycemia in laboratory findings may be the early signs of mortality in patients with methyl alcohol poisoning. Therefore, patients with these signs should be followed up more closely and treated.

Keywords: Emergency Treatment, Laboratory Findings, Methyl Alcohol Poisoning, Mortality Rate.

Acil Servise Başvuran Metil Alkol Zehirlenmelerinin Geriye Dönük Analizi

ÖZET

Amaç: Metil alkol zehirlenmesi önemli bir mortalite ve morbidite nedeni olmaya devam etmektedir. Bu zehirlenme halen acil servislere başvurunun önemli nedenlerinden biridir. Bu çalışmada acil serviste metil alkol zehirlenmesi tanısı alan hastaların başvuru şikayetlerini, laboratuvar bulgularını, tedavi yöntemlerini, klinik sonuçlarını ve mortaliteyi etkileyen faktörleri incelemeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif tanımlayıcı çalışmada 1 Haziran 2018 ile 1 Haziran 2020 tarihleri arasında alkol zehirlenmesi nedeniyle acil servisimize başvuran hastalardan metil alkol zehirlenmesi tanısı düşünülen hastaları inceledik.

Bulgular: Çalışmaya etil ve metil alkol alımı ve buna bağlı etkiler nedeniyle acil servise başvuran 411 kişiden metil alkol zehirlenmesi olan 20 kişi (%4.86) dahil edildi. Hastaların yaş ortalaması 47.35±14,2 yıl olup, %85'i (n=17/20) erkekti. Hastaların başvuru semptomları incelendiğinde %70'inde görme problemi, %60'ında kusma, %45'inde nefes darlığı ve %40'ında bilinç değişikliğinin olduğu görüldü. Araştırmada %18.2(n=2/11) kadın ve %81.8(n=9/11) erkekte ölüm saptanmış olup, ölüm oranı %55(n=11/20) olarak hesaplanmıştır.

Sonuç: Metil alkol zehirlenmesi olan hastalarda klinik ve laboratuvar bulgularında; görme sorunları, hipotansiyon ve koma, yüksek anyon açıklı metabolik asidoz, belirgin ozmolar boşluk, laktat düzeyinde artış ve hiperglisemi varlığı mortalitenin erken belirtileri olabilir. Bu nedenle bu belirtileri olan hastalar daha yakın takip ve tedavi edilmelidir.

Anahtar Kelimeler: Acil Servis, Laboratuvar Bulguları, Metil Alkol Zehirlenmesi, Ölüm Oranı.

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INTRODUCTION

Methyl alcohol (methanol), also known as wood alcohol, is a raw material that is taken intentionally, accidentally, or for a suicidal purpose and turns into a toxic substance in the body due to its intoxicative properties and easy producibility (1). In industries, methyl alcohol can be found in cleaning materials, carburetor cleaners, antifreeze, photocopying liquids, chemicals such as paint and wax, glass cleaning solutions, model aircraft fuels, modified cars, alternative fuels, and homemade moonshine (2). It is reported that the use of hand disinfectants and cologne due to the COVID-19 outbreak may cause methyl alcohol poisoning (3). Methyl alcohol poisoning (MP) is an important emergency that can lead to severe morbidity and mortality (4). Clinical diagnosis is usually difficult, and the diagnosis of poisoning is difficult, and it is often diagnosed late (4,5). In recent years, the number of poisonings and resulting deaths due to the illegal production or sale of MA for liquor has increased substantially. Therefore, the patient's complaints and laboratory findings may be effective in predicting possible morbidity and mortality. Also, it is crucial to diagnose and treat this poisoning early.

This study aimed to examine the demographic data, admission complaints, laboratory findings, treatment approaches and examine the factors affecting the mortality of the patients, who were diagnosed with MP in the our emergency department(ED) and started treatment, and the correlation of these findings with clinical outcomes.

MATERIAL AND METHODS

In this retrospective descriptive study, patients with MP were screened through the hospital information management system (HBYS) and the archive records of the ED and intensive care unit(ICU). The International Classification of Disease (ICD) 10 coding system was used to select patients(T51.0, T51.1, T51.9, X45, X65, Y15, Y91, Y91.0, Y91.1, Y91.2 and Y91.3 codes was used). The patients included in the study were selected from among the patients who applied to the tertiary ED of Kayseri City Hospital between June 1, 2018, and June 1, 2020. A total of 411 patients were found to have used alcohol. Individuals with incomplete data in the patient file, individuals with ethyl alcohol or other alcohol intake, individuals referred to another institution, and individuals under the age of 18 were excluded from the study. As a result, a total of 391 patients were excluded. The study included 20 patients who were assumed to be poisoned due to MA intake based on the anamnesis taken from patients or their relatives in light of the information obtained from patient files.

Blood samples taken from the all patients were recorded. Venous blood gas samples taken from the patients were recorded 3 times (at the patient's admission, at the end of antidote therapy, and before discharge or mortality). According to the blood results obtained, anion gap, base deficit, osmolarity, and osmolar gap were calculated. The diagnosis of MP was established with the history of alcohol intake, presence of MP findings, pH <7.3 in blood gas and serum bicarbonate <20 mmol/L (6-8). After the patients were diagnosed and provided with initial treatment in the ED, they were found to continue their follow-up in the internal service or ICU.

Due to the absence of an MA kit in our hospital at the time of the study, the MA level could not be measured. The patients' routes of alcohol intake, admission complaints, vital and physical examination findings, ECG findings, history, the month of admission, the status of taking other drugs or ethyl alcohol together with MA, and laboratory results were recorded in the patient follow-up form. Moreover, treatment methods applied to the patients, changes in their laboratory values during hospitalization, their lengths of hospital stay, and clinical outcomes were also recorded. The obtained data were analyzed.

The study was approved by the Kayseri City Hospital Ethics Committee with the date and number 25.06.2020/99.

Statistical Analyses: Descriptive statistics were presented with frequency, percentage, mean and standard deviation values. The Mann-Whitney U test was conducted to analyze the measurements according to the study groups. Chi-squared analysis was performed to examine the relationships between the proportional values according to the groups. In the study, the Friedman test was carried out to examine the difference of the 1st, 2nd, and 3rd laboratory measurements. P-values less than 0.05 were considered significant in the study. SPSS 25.0 program was used for analyses.

RESULTS

In this study, the rate of MP in people with methyl, ethyl and other alcohol intake was calculated as 4.86% (n=20/411). The mean age of the patients was found to be 47.35±14.2 years (range: 22-66 years). The patients' mean Glaskow Coma Scale(GCS) value was 10.95±4.62, mean systolic blood pressure (SBP) value was 114.9±23.66 mmHg. The patients' mean length of hospital stay was 9.05±10.07 days. Upon reviewing by group, it was observed that the patients' ages, SBP measurements, pulses, respiratory rates, saturation, and durations of hospital stay were not significantly correlated with their survival levels (p>0.05) (Table 1).

Table 1. Comparison of vital findings and lengths of hospital stay by group

Variables	Total patients	Group		*P*-Value*
		Discharged	Exitus	
	Mean±SD	Mean±SD	Mean±SD	
Age	47.35±14.2	45.89±16.61	48.55±12.6	0.82
GCS	10.95±4.62	14.67±0.71	7.91±4.18	0.01*
SBP	114.9±23.66	118.89±17	111.64±28.39	0.36
Pulse	91.65±15.64	93.22±10.23	90.36±19.42	0.29
Respiratory rate	18.00±3.93	18.56±3.57	17.55±4.32	0.70
Saturation (Spo2)	94.4±5.31	96.44±3.57	92.73±6.03	0.12
Length of hospital stay (days)	9.05±10.07	4.78±4.18	12.55±12.19	0.21

*GCS: Glasgow Coma Scale, SBP: Systolic Blood Pressure *Significant difference at the 0.05 level*

Upon examining the patients' admission symptoms, 75% (n=15) were observed to have visual problems, 60% (n=12) complaints of vomiting, 45% (n=9) shortness of breath, 40% (n=8) changes in consciousness. Of the patients, 50% (n=10) were conscious, 15% (n=3) were confused, 10% (n=2) were lethargic, and 25% (n=5) were in a coma at the admission to the hospital. Of the patients, 10%(n=2) were observed to have normal physical examination findings. The mortality rates of the group with reduced vision, in a coma and with change in consciousness were found to be higher (p=0.02 and p=0.01). Of the patients, 75%(n=15) had reduced vision, and 40%(n=8) had pathology in the neurological examination. The incidence of coma, hypotension, and optic disc hyperemia was seen to be higher in the exitus group (p<0.05). The presence of pancreatitis was revealed in 40% of the patients at their first admissions. The mortality rates of the patients with pancreatitis were observed to be higher (p=0.03)(Table 2).

Table 2. Comparison of the patients' exitus statuses according to admission symptoms and examination findings

Complaints		Total	Group		*P*- Value*
			Discharged	Exitus	
		n(%)	n(%)	n(%)	
Reduced vision	Yes	15(75)	5(55.6)	10(90.9)	0.02*
	No	5(25)	4(44.4)	1(9.1)	
Pathological finding in the neurological examination	Yes	8(40)	0(0)	8(72.7)	0.09
	No	12(60)	9(3)	3(27.3)	
Coma	Yes	8(40)	0(0)	8(72.7)	0.01*
	No	12(80)	9(100)	2(18.2)	
Nausea-vomiting	Yes	12(60)	5(55.6)	7(63.6)	0.15
	No	8(40)	4(44.4)	4(36.4)	
Shortness of breath-respiratory distress	Yes	9(45)	1(11.1)	8(72.7)	0.01*
	No	11(55)	8(88.9)	3(27.3)	
Change in consciousness	Yes	8(40)	0(0)	8(72.7)	0.01*
	No	12(60)	9(100)	3(27.3)	
Agitation	Yes	1(5)	0(0)	1(9.1)	0.26
	No	19(95)	9(100)	10(90.9)	
Hypotension	Yes	4(20)	0(0)	4(36.4)	0.03*
	No	16(80)	9(100)	7(63.6)	
Mydriasis	Yes	9(45)	4(44.4)	5(45.5)	0.91
	No	11(55)	5(55.6)	6(54.5)	
Retinal Edema	Yes	13(65)	5(55.6)	8(72.7)	0.16
	No	7(35)	4(44.4)	3(27.3)	
Optical Disc Hyperemia	Yes	11(55)	3(33.3)	8(72.7)	0.02*
Abdominal pain	Yes	2(10)	0(0)	2(18.2)	0.12
	No	18(90)	9(0)	9(81.8)	

**Significant difference at the 0.05 level*

Of the patients, 15% (n=3) were female, and 85% (n=17) were male. Concerning the admission times of the patients, they presented to the hospital rather in March 25% (n=5). Thirty percent of patients(n=6) produced MA at home, 50% (n=10) of patients drank cologne, and 20%(n=4) of patients bought from a small shop. 30% (n=6) of patients were found to take ethanol together with MA. Mortality rates differed according to the way of procuring MA. Mortality rates of the individuals who drank cologne and the patients who took ethanol together with MA were high (p=0.03). In addition to MA, 30%(n=6) patients were observed to take ethanol, and 5%(n=1) psychostimulant and other drugs. Mortality rates of the patients with a history of alcohol abuse, psychiatric illnesses, liver failure, and kidney failure were not different (p>0.05). The patients were given bicarbonate 55% (n=11), thiamine %70 (n=14), ethanol %80 (n=16), and calcium folinate %70 (n=14) treatment together with fluid therapy. Eighty percent of the patients were on hemodialysis. Mortality rates of the group

treated with bicarbonate and hemodialysis were found to be higher (p=0.01). Of the patients, 20% (n=4) were followed up in the wards, but 80% (n=16) were followed up in ICUs. Twenty five percent of the patients were discharged after ICU follow-up. Of the patients, 45% (n=9) were discharged in total, but 55% (n=11) of the patients died (Table 3). Among the patients' laboratory values, WBC, MPV, Cr, Glucose, K, AST, Lipase, CK, and Troponin measurements were found to be higher in the exitus group (p<0.05). (Table 4).

Table 3. Comparison of patient characteristics, time of application, way of methyl alcohol procurement, concomitant ethanol intake, treatment method and clinical outcomes

Variables			**Group**		***P*-Value***
			Discharged	**Exitus**	
			n(%)	n(%)	
Gender	Female	3(15)	1(11.1)	2(18.2)	0.56
	Male	17(85)	8(88.9)	9(81.8)	
	Total	20(100)	9(45)	11(55)	
Application month	October	1(5)	0(0)	1(9.1)	-
	June	2(10)	1(11.1)	1(9.1)	
	November	2(10)	2(22.2)	0(0)	
	March	5(25)	3(33.3)	2(18.2)	
	May	3(15)	1(11.1)	2(18.2)	
	April	2(10)	0(0)	2(18.2)	
	January	2(10)	1(11.1)	1(9.1)	
	February	2(10)	1(11.1)	1(9.1)	
	July	1(5)	0(0)	1(9.1)	
Way of procurement	Made at home	6(30)	4(44.4)	2(18.2)	0.03*
	Drank cologne	10(50)	3(33.3)	7(63.6)	
	Bought from a small shop	4(20)	2(22.2)	2(18.2)	
Was ethanol taken together with MA?	Yes	6(30)	4(44.4)	2(18.2)	0.03*
	No	14(70)	5(55.6)	9(81.8)	
Treatment Method					
Sodium Bicarbonate	Yes	11(55)	2(22.2)	9(81.8)	0.01*
	No	9(45)	7(77.8)	2(18.2)	
Thiamin	Yes	6(30)	2(22.2)	4(36.4)	0.21
	No	14(70)	7(77.8)	7(63.6)	
Ethanol	Yes	16(80)	6(66.7)	10(90.9)	0.08
	No	4(20)	3(33.3)	1(9.1)	
Fomepizole	Yes	0(0)	0(0)	0(0)	-
	No	20(100)	9(100)	11(100)	
Calcium Folinate	Yes	14(70)	7(77.8)	7(63.6)	0.21
	No	6(30)	2(22.2)	4(36.4)	
Hemodialysis	Yes	16(80)	5(55.6)	11(100)	0.01*
	No	4(20)	4(44.4)	0(0)	
Clinical outcome					
Hospitalization in the ward	Yes	4(20)	4(44.4)	0(0)	0.01*
	No	16(80)	5(55.6)	11(100)	
Hospitalization in the ICU	Yes	16(80)	5(55.6)	11(100)	0.01*
	No	4(20)	4(44.4)	0(0)	
Discharged	Yes	9(45)	9(100)	0(0)	-
	No	11(55)	0(0)	11(100)	
Exitus	Yes	11(55)	0(0)	11(100)	-
	No	9(45)	9(45)	0(0)	

*MA: Methyl Alcohol, ICU: Intensive Care Unit *Significant difference at the 0.05 level*

Table 4. Laboratory values of the patients at the time of admission

Variables	Total	Group		*P*-Value*
		Discharged	Exitus	
	Mean±SD	Average ±SD	Mean±SD	
WBC (Ref:4.5-10,000)	11.92±5.53	9.07±3.48	14.25±5.93	0.02*
Hg (Ref:13-17g/dL)	14.54±2.71	14.73±3.03	14.37±2.55	0.73
PLT (150-450*thousand)	261.8±148.05	252.33±59.95	269.55±196.54	0.47
N/L ratio (%)	4.12±3.49	3.4±1.73	4.71±4.46	0.73
NRBC (%)	0.15±0.36	0.06±0.07	0.23±0.47	0.93
MPV (Ref:9-12 fL)	10.04±1.11	9.49±0.89	10.49±1.11	0.04*
BUN (Ref:6-20 mg/dL)	14.43±11.72	11.46±3.94	16.85±15.3	0.88
Cr (Ref:0.70-1.20 mg/dL)	1.21±0.77	0.83±0.27	1.52±0.91	0.01*
Glucose (Ref:70-110 mg/dL)	172.75±75.13	135.33±61.68	203.36±73.41	0.04*
Na (Ref:136-145 mmol/L)	137.6±6.13	136.22±3.03	138.73±7.8	0.22
K (Ref:3.5-5.1 mmol/L)	4.70±0.78	4.19±0.61	5.11±0.67	0.01*
Cl (Ref: 98-107 mmol/L)	100.75±7.87	102.11±3.3	99.64±10.29	0.65
AST (Ref:0-40 U/L)	74.35±66.18	38.22±31.16	103.91±73.55	0.02*
ALT (Ref:0-41 U/L)	39±25.85	28.67±19.53	47.45±28.1	0.14
Amylase (Ref: 28-100 U/L)	169.4±256.48	95.67±35.85	229.73±339.2	0.14
Lipase (Ref:13-60 U/L)	212.6±554.14	47.11±29.93	348±733.42	0.01*
CK (Ref:0-190 U/L)	361.8±667.78	131.33±56.43	550.36±870.52	0.01*
CKMB (Ref:0-36 U/L)	42.15±21.36	39.56±25.17	44.27±18.68	0.23
Troponin I (Ref:0-0.30 µg/L)	0.72±2.18	0.21±0.34	1.14±2.92	0.01*
Ethanol (mg/dL)	17±37.7	35.33±51.32	2.00±6.63	0.05

*WBC, white blood cell; Ref, reference interval; Hg, hemoglobin; PLT, platelet; N/L, neutrophil/lymphocyte; NRBC, nucleated red blood cells; MPV, mean platelet volume; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; CKMB, creatinine kinase myocardial band, *Significant difference at the 0.05 level*

In the patients' blood gas analysis, mean pH, HCO3, PCO2, PO2, lactate values, and osmolarities did not differ over time. Base deficit(BD) and osmolar gap were initially lower (p=0.01). The anion gap was higher in the beginning (p=0.01). The patients' first measured blood gas pH, HCO3, and BD base deficit measurements were lower in the exitus group, whereas PO2, anion gap, and lactate values were higher in the surviving group(p=0.01). The patients' second measured blood gas pH, HCO3, and anion gap levels were observed to be lower in the exitus group (p<0.05). BD was at higher levels in the exitus group (p=0.04). The patients' third measured blood gas pH, HCO3, and BD base deficit measurements were lower in the exitus group, while anion gap, lactate, and osmolarity values were at higher levels in the exitus group(p=0.01) (Table 5).

Table 5. Examination of the patients' blood gas measurements according to their survival status

Variables		Group		*P*-Value*
		Discharged	Exitus	
		Mean±SD	Mean±SD	
pH	Measurement 1	7.25±0.17	6.96±0.21	0.01*
	Measurement 2	7.38±0.06	7.14±0.17	0.01*
	Measurement 3	7.41±0.04	7.20±0.22	0.01*
HCO3	Measurement 1	17.87±6.09	8.71±5.6	0.01*
	Measurement 2	21.89±2.88	14.78±6.19	0.02*
	Measurement 3	25.71±3.09	17.08±6.26	0.01*
PCO2	Measurement 1	37.89±8.28	33.91±15.53	0.14
	Measurement 2	36.74±5.87	43.06±19.11	0.34
	Measurement 3	41.53±9.34	46.87±24.98	0.68
PO2	Measurement 1	39.46±15.81	70.85±26.37	0.01*
	Measurement 2	45.72±15.17	54.2±24.98	0.57
	Measurement 3	44.23±25.05	52.68±28.29	0.68
BD	Measurement 1	-7.86±8.52	-24.43±9.28	0.01*
	Measurement 2	-2.44±5.62	-13.25±10.31	0.04*
	Measurement 3	2.24±4.11	-6.80±9.94	0.02*
Anion Gap	Measurement 1	21.91±7.89	34.49±5.93	0.01*
	Measurement 2	16.13±4.27	24.76±6.6	0.01*
	Measurement 3	11.33±2.94	24.25±6.34	0.01*
Lactate	Measurement 1	3.27±3.8	9.73±6.53	0.01*
	Measurement 2	2.86±2.40	5.72±4.24	0.14
	Measurement 3	2.28±3.37	8.49±7.59	0.01*
Osmolarity	Measurement 1	291.11±13.59	295.09±17.92	0.38
	Measurement 2	301.67±8.62	292.82±11.91	0.12
	Measurement 3	286.32±5.03	310.09±25.89	0.01*
Osmolar gap	Measurement 1	-19.31±17.8	-14.91±17.92	0.24
	Measurement 2	22.33±8.96	30±10.92	0.06
	Measurement 3	25.33±4.12	18.36±17.71	0.42

*pH: potential hydrogen, HCO3: bicarbonate, PCO2: partial carbon dioxide, PO2: partial oxygen BD: base deficit (reference range: [(-2.5) - (+2.5)], Anion Gap: calculated with the formula [(Na+K) - (Cl+HCO3)] (reference range: 8-12 mEq/L). Osmolarity: calculated with the formula [2*Na+Glucose/18+BUN/2.8+Ethanol/4.6] (reference range: 275-285 mOsm/L), Osmolar gap: calculated with the formula [(measured osmolarity-calculated osmolarity) + (Add 2.17 mOsm/L to the osmolar gap for every 10 mg/dl ethanol increase)] (target value: 310 mOsm/L). *Significant difference at the 0.05 level*

DISCUSSION

In recent years, an increase has been observed in admissions to EDs due to MP and relevant complications owing to reasons such as the increase in the prices of ethyl alcohol products and the increase in the illegal production of MA (4,9). Cases of poisoning with dermal exposure to MA have also increased with the increase in the use of cologne and hand disinfectants along with the COVID-19 outbreak (10). Rather than MA itself, its metabolites, such as formaldehyde, formic acid, and formate, are toxic (3). Despite improvements in treatment opportunities, the rates of morbidity and mortality in MP are still high. Because the findings of MP differ from person to person, the diagnosis is established late, thus, the treatment is initiated late, which contributes to increased morbidity and mortality rates (3,4,9). It is of great importance to quickly diagnose and treat this poisoning in EDs. In our study, the rate of people diagnosed with MP was 4.86%. The majority of the individuals included in our study were male (85%). The mean age of the patients was calculated as 47.35±14.2 years(range: 22-66 years). Of the patients with signs of poisoning, 80% were monitored in ICUs. Mortality rate was 55% (n=11). Among people who consumed alcohol, the mortality rate related to MA was calculated as 2.67%. In the literature, it is seen that MP and resulting deaths have tended to increase in numerous people, particularly during the COVID-19 pandemic in Asian countries, while they are generally in the form of case reports in European countries (11). In a study, Aghababaeian H. et al. stated that 768 people presented to ED in Iran in 2018 due to MP, 10.1% (76 people) died, and the ages of the poisoned people varied between 25-36 years (12). Another study from Turkey reported that 39 male and 8 female patients between the ages of 18-67 presented to a tertiary care hospital between 2016 and 2020 due to MP, and 12.7%(n=6) of these patients died (13). Similar to the literature, MP is usually observed in the young age group in our study. The rate of mortality caused by this poisoning differs according to countries. In our study, people were found to mostly take MA by drinking cologne 50% (n=10). The fact that 30% of the patients took MA together with ethanol. In a study conducted in our country, the sources of MA were cologne (72.6%) in 113 patients with MP (14). In our study, the route of exposure to MA was mostly cologne drinking and mortality was observed to be higher in people with cologne-related MP. Cologne, which is inexpensive and easily accessible. Some people who cannot afford to buy alcohol in our country try to meet their alcohol needs by drinking cologne. Cologne produced in an uncontrolled manner can also contain MA. This type of cologne with MA content can cause poisoning and death, as revealed in our study.In the literature, MP is observed every month of the year, but an increase is observed in the number of poisoned patients in some months. In their study, Hadipourzadeh M. et al. mentioned an increase in MP cases in November, January, and March (15). In our study, the number of poisoning cases was higher in winter and spring. On a monthly basis, the highest number of applications was in March (n=5).The half-life of MA dispersion is about 8 minutes, which is longer than the absorption half-life (16). Clinical signs of pure MA toxicity start from 0.5 to 4 hours following ingestion and include gastrointestinal disorders and central nervous system (CNS) suppression (17). In our study, the most common first three admission complaints in patients were visual problems, nausea-vomiting, and shortness of breath, respectively. The occurrence of MP findings is associated with the amount of alcohol taken, the time of intake, and the route of exposure (18,19).The patients' vital signs were generally stable at first time in our study. 75% of the patients had reduced vision. In the literature, it is reported that ocular symptoms may occur in half of the poisoned patients, and these symptoms usually develop 6 hours after taking MA (20,21). In MP, pupils are mydriatic and reported to give delayed response to light or be unresponsive (17). In their study, Brahmi N. et al. stated that the clinical symptoms of patients with MP included central nervous system symptoms (69%), gastrointestinal complaints (87%), and visual impairment (69%) (20). Similar to the literature, 75% of the patients had eye-related findings in our study. Depending on the dose, MA can lead to intoxication and CNS depression. Usually, serum MA concentrations of 25-50 mg/dL may accompany toxicity (22). In their study, Brahmi N et al. reported that mortality was more common in patients with vision loss, in shock and coma (20). In our study, changes in consciousness due to influence in the CNS were observed in 40% of the patients, 15% were confused, 10% were lethargic, and 25% were in a coma at their first admission. Likewise, mortality was higher in patients with visual problems, hyperemia of the optic disc, hypotension, and in a coma in our study. This was thought to possibly result from the damage to tissues and organs due to increased MA in the blood and blood acidosis elevated by its metabolites. In patients with anion gap acidosis of unknown cause and mostly with a history of alcohol intake, the possibility of MP is first suspected. Unless otherwise is suggested by clinical evidence, it is important to exclude metabolic acidosis with ketoacidosis and high lactate concentration, which are the most common causes of anion gap acidosis, before initiating MP treatment in these patients (6). In some hospitals, there are almost no laboratory facilities to evaluate the blood levels of toxic alcohol and its metabolites. In such cases, the diagnosis of MP can be established with anamnesis, clinical and laboratory findings (6,7). It is stated in the literature that

clinicians' clinical MP evaluations should be based on clinical history, physical findings, anion gap, and osmolal gap when MA levels cannot be checked (8). In our study, MP was diagnosed with anamnesis, clinically and laboratory findings. Since there was no methanol kit in our hospital at the time of our study, the MA level could not be checked. In the study by Desai T et al., laboratory research included a complete hemogram, hematocrit level, plasma bicarbonate levels, serum electrolyte levels, complete liver and kidney function test results, arterial blood gas analysis, blood methanol concentrations, and serum proteins in patients with suspected MP (23). In our study, blood parameters were compared after the patients were divided into two groups as discharged and exitus. As a result, there was a significant difference in WBC, MPV, Cr, Glucose, Potassium, AST, Lipase, CK, and Troponin I measurements according to blood analysis in the exitus group compared to the discharged group. In the patients' blood gas analysis, mean pH, HCO3, PCO2, PO2, lactate values, and osmolarities did not differ over time. BD and osmolar gap were lower, and the anion gap was higher in the beginning. Concerning serial blood gas measurements, there was a significant difference in pH, HCO3, BD and lactate values. In the last measurement, there was a significant difference in mean osmolarity values of the exitus group compared to the discharged group. Unlike the present studies, blood gases, lactate, osmolality, osmolar gap, and anion gaps were checked 3 times in total, first at the time of admission, at the end of antidote therapy, and lastly before discharge or exitus. In their study, Kacer I et al. reported that the mean pH value was 7.17±0.7, the mean HCO3 value was 10.55±7.02 mmol/L, and the mean glucose value was 156±118 mg/dL(13). In our study, the mean pH value in the blood gases first taken from the patients was 7.25±0.17 in the discharged group and 6.96±0.21 in the exitus group. The mean HC03 was 17.87±6.09 in the discharged group and 8.71±5.6 in the exitus group. The mean glucose value of all patients was 203.36±73.41. The mean glucose values of the exitus group were found to be higher. In their study, Kute et al. reported that pH ≤6.9 was highly associated with mortality (24). In our study, the mean pH value of the exitus group was 6.96±0.21 in the first blood gas analysis, and the values were significantly lower both in the first and the other two measurements compared to the discharged group. Moreover, in our study, HCO3 values were also measured significantly lower in the exitus group in all three measurements in blood gas analysis. Low pH and HCO3 values in the blood gas measured at the first admission and during follow-up can be markers of mortality in MP. In their study, Zahra N et al. stated that lactate values might increase in MP (6). In our study, the patients' lactate levels measured when they first arrived were 3.27±3.8 in the discharged group and 9.73±6.53 in the exitus group. Considering these values, it can be interpreted that high lactate levels in MP can be a marker of mortality. However, there is a need for more comprehensive studies on this subject. It has been reported that, in MP, patients with abdominal pain should also be tested for the possibility of associated hepatitis and pancreatitis, and hyperglycemia may also play a role in the development of acute pancreatitis (6,25). In our study, amylase and lipase were routinely checked in all patients against the risk of pancreatitis. In the exitus group, both amylase and lipase levels were found to be significantly higher. According to these results, the risk of mortality may be higher in MP if pancreatitis has started to develop. Due to the quick absorption of alcohol, the use of gastric lavage or activated charcoal does not affect poisoning in MP. Treatment of MP is based on the use of an antidote (fomepizole or ethanol) to prevent the oxidation of methanol, folic acid to facilitate formic acid catabolism, and hemodialysis for accelerating the removal of methanol and acidosis modification (5). Moreover, sodium bicarbonate (NaHCO3) is recommended to fix acute acidosis (pH<7.3) (26). Fomepizole is more likely to inhibit alcohol dehydrogenase (ADH) and has a longer action duration. Its use is also easier. Ethanol binds to ADH more than toxic alcohol (3). The presence of ethanol inhibits the formation of toxic metabolites, and it has been reported that ethanol may be adequate for ADH blockade if fomepizole is not present. Hemodialysis eliminates both MA and its toxic metabolites from the blood and fixes acid-base disorder. Within the first few hours after dialysis, MA concentrations may be elevated due to redistribution of MA. Therefore, dialysis should be continued until the MA level drops to zero and acidosis disappears (18). Folinic acid (calcium folinate) makes the hydrolysis of formic acid, the toxic intermediate of MA, to carbon dioxide and water easier. Thus, lactate formation is reduced as a result of deterioration of mitochondrial functions caused by formic acid accumulation in tissues and a decrease in the NAD +/NADH ratio (5). Thiamine can be administered as a supportive treatment in people with CNS and eye findings due to its neuroprotective effect (27). In our study, 80% of the patients were administered ethanol, 70% thiamine, 70% calcium folinate, and 55% sodium bicarbonate, and 80% underwent hemodialysis. Fomepizole could not be started as antidote therapy for the patients since it was expensive and limited in number in the hospital. Instead, 10% IV ethanol treatment was started in all patients as antidote therapy. Patients with clinically severe signs of toxicity and high anion gap deep metabolic acidosis underwent hemodialysis, and ethanol treatment was continued by monitoring the blood levels. Interestingly, mortality was higher in patients who were given sodium bicarbonate treatment and underwent hemodialysis in our study. It was

anticipated that there might be an increase in mortality rates in these patients due to their deep acidosis and higher toxicity levels.

In our study, patients who were found to have ethanol in blood analysis together with MA generally had symptoms such as abdominal pain, nausea-vomiting, and headache in the early period. However, more serious findings such as visual problems, lethargy, and coma were observed in the later period since ethanol remaining in the blood was not enough to inhibit alcohol dehydrogenase. In other words, the concomitant intake of ethanol and MA may have masked MP and prevented the appearance of symptoms.

CONCLUSIONS

There has been an increase in patients' admission to EDs due to MP in recent years. The early diagnosis of MP and quick initiation of its treatment is extremely important to reduce morbidity and mortality. Especially cologne and hand disinfectants can cause toxicity since they may contain MA. The early diagnosis of MP and quick initiation of its treatment are extremely important to reduce morbidity and mortality. It should be remembered that the presence of visual problems, hypotension, and coma in clinical findings, high anion gap metabolic acidosis (pH<7.25, low HCO3 level), marked osmolar gap, increase in lactate level, and hyperglycemia in laboratory findings can be the signs of mortality in patients diagnosed with MP. Therefore, the early treatment and close follow-up of patients with the said findings are required.

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RESEARCH ARTICLE

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Evaluation of Health Promoting Lifestyle Habits during Pandemic Period, a Cross Sectional Study

ABSTRACT

Objective: The COVID-19 pandemic imposed lifestyle changes. The aim of this study was to evaluate the health-promoting lifestyle habits of individuals who applied to a primary care center during the pandemic period.

Methods: This descriptive and cross-sectional study was conducted with the voluntary participation of 524 individuals. The data was collected through a research questionnaire form and the Health Promoting Lifestyle Scale (HPLS).

Results: Women accounted for 58.2% (n=305) of all participants, 45.2% of them (n=237) had chronic disease and 32.1% (n=168) were smoking. Mean age was 41.26±14.28 (min:18, max:75) years old. Among these participants, %53.2 had equal income to their expenses (n=279), 52.3% experienced sleep pattern changes (n=274), 35.7% had COVID-19 disease and 66.6% vaccinated for COVID-19. The mean HPLS score was 162.75±8.10 points. Interpersonal relationships, stress management and total HPLS scores were higher in women ($p<0.05$). Physical activity, nutrition, stress management, total scores were higher in those without chronic diseases. Health responsibility scores of those vaccinated by COVID-19 vaccine, was higher ($p=0.04$). Stress management scores were lower in those with decreased sleep duration during the pandemic ($p=0.050$).

Conclusions: This study revealed that the participants' HPLS scores were low. It is necessary to continuously develop and support healthy lifestyle behaviors in areas such as physical activity, nutrition, spiritual development, and health responsibility. In the pandemic period, while we better understood the importance of protecting health, studies that will contribute the development of healthy lifestyle behaviors should be accelerated.

Keywords: Health Promotion, Physical Activity, Nutrition, Stress Management, COVID-19 Pandemic.

Pandemi Döneminde Sağlığı Geliştirici Yaşam Alışkanlıklarının Değerlendirilmesi: Kesitsel Bir Çalışma

ÖZET

Amaç: COVID-19 pandemisi bazı yaşam tarzı değişikliklerini zorunlu kıldı. Bu çalışmada, pandemi döneminde birinci basamak sağlık merkezine başvuran bireylerin sağlığı geliştirici yaşam tarzı alışkanlıklarının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Tanımlayıcı ve kesitsel tipteki bu araştırma 524 kişinin gönüllü katılımıyla gerçekleştirilmiştir. Veriler, sosyo-demografik özellikler anket formu ve Sağlığı Geliştirici Yaşam Tarzı Ölçeği aracılığıyla toplanmıştır.

Bulgular: Katılımcıların %58,2'sini (n=305) kadınlar oluşturuyordu, %45,2'sinin (n=237) kronik hastalığı vardı ve %32,1'i (n=168) sigara kullanıyordu. Ortalama yaş 41,26±14,28 olup, %53,2'sinin geliri giderlerine eşitti (n=279). Katılımcıların %52,3'ü pandemi döneminde uyku düzeninde değişiklik yaşadığını (n=274), %35,7'si COVID-19 hastalığı geçirdiğini ve %66,6'sı COVID-19 aşısı olduğunu belirtti. Sağlığı geliştirici yaşam tarzı ölçeğinden ortalama 162,75±8,10 puan alındı. Kişilerarası ilişkiler, stres yönetimi ve toplam puanlar kadınlarda daha yüksekti ($p<0.05$). Fiziksel aktivite, beslenme, stres yönetimi ve toplam puanlar kronik hastalığı olmayanlarda daha yüksekti. COVID-19 aşısı yaptıranların sağlık sorumluluğu alma puanları daha yüksekti ($p=0.04$). Pandemi sırasında uyku süresi azalmış olanlarda stres yönetimi skorları daha düşüktü ($p=0,050$).

Sonuç: Bu çalışma, katılımcıların sağlığı geliştirici yaşam tarzı ölçeği puanlarının düşük olduğunu ortaya koydu. Fiziksel aktivite, beslenme, ruhsal gelişim, sağlık sorumluluğu alma gibi alanlarda sağlıklı yaşam biçimi davranışlarının sürekli geliştirilmesi ve desteklenmesi gerekmektedir. Pandemi döneminde sağlığı korumanın önemi daha iyi anlaşılmışken sağlıklı yaşam biçimi davranışlarının geliştirilmesine katkı sağlayacak çalışmalara hız verilmelidir.

Anahtar Kelimeler: Sağlığı Geliştirme, Fiziksel Aktivite, Beslenme, Stres Yönetimi, COVID-19 Pandemisi.

INTRODUCTION

The current pandemic period has hampered progress towards a healthy lifestyle by necessitating social isolation measures (1). Social distancing, self-isolation, and quarantine posed the mental health threat (2).

Changeable lifestyle behaviors as an unhealthy diet, physical inactivity, cigarette, alcohol, and substance use increase the incidence of non-communicable diseases and cause worsening and progression of existing diseases (3). These are simultaneously accepted as risk factors besides chronic disease and its uncontrolled course for negative consequences of COVID-19 disease (4).

Since the pandemic struggle has occupied health institutions for two years, there have been inevitable disruptions in the follow-up of chronic diseases and delays in new diagnoses. Ultimately, the pandemic has increased the global disease burden of non-communicable diseases (5).

The quarantine process has also been associated with many adverse psychological effects. Fear of infection, frustration, boredom, obsessive-compulsive symptoms, insufficient information, fear of stigmatization, and financial losses are factors that negatively affect mental health (6).

There are also studies reporting that the quarantine process by reducing outdoor activities enables the development of healthier habits to benefit more from the various social support systems. As a result of education and advanced level of health literacy in developed countries, adaptation to the quarantine process has been easier, and stress management has progressed more successfully (7).

Healthy lifestyle behaviors include nutrition, physical activity, regular sleep, stress management, avoidance of risky behaviors, and quality social relationships. This well-rounded approach will increase disease-free lifespan and improve quality of life in all aspects (8). In this regard, health-promoting behaviors should be expanded while the pandemic is still ongoing.

Health-promoting behaviors require a comprehensive and holistic approach (9). The process begins when individuals realize that they can increase their control over health-determining factors. It should be aimed to make these behavior patterns a habit (9). Lifestyle affects health significantly, and morbidity and mortality of chronic diseases can be reduced with healthy lifestyle changes (10).

In this study we aimed to evaluate the health-promoting lifestyle habits of people who applied to a primary care center and investigate how these habits were affected by the changing living conditions during the pandemic.

MATERIAL AND METHODS

Study Design and Sampling: This cross-sectional study included the individuals applying to a primary care unit and agreed to participate the study between 1 March and 1 June 2021. Based on the number of the registered population served in the Primary Care Unit, the sample size was calculated with the OpenEpi v3.01 program and was found to be 351 at a 5% significance level, 95% confidence interval, and 95% power. 524 participants were included in the study. Written informed consents of the participants were obtained after informing about the purpose of the study. Those with any psychiatric disease were excluded from the study.

Socio-demographic data were collected and Health Promoting LifeStyle Scale (HPLS) were used. The questionnaires were applied by face-to-face interview method. Subdimensional and total HPLS scores were calculated.

Ethical Approval: This study received approval from the Necmettin Erbakan University Non-Invasive Resarch Ethics Committee (2021/3240-5598). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Socio-Demographic Characteristics Questionnaire: Participants were asked to report their age, gender, marital status, education level, economic situation, chronic illness, change in their sleeping habits, coronavirus vaccination status and COVID-19 diagnosis. They were also asked whether they have a health care worker relative and whether they had any acquaintances diagnosed with COVID-19 infection or died due to COVID-19.

The Health-Promoting Lifestyle Scale-II (HPLS): Health-Promoting Lifestyle Scale-II, which was developed by Walker and Hill-Polerecky, and validated into Turkish by Pınar et al, was used in the study (11). The scale measures the health-promoting lifestyle behaviors by fifty-two items and six sub-dimensions. These sub-dimensions are; health responsibility, physical activity, nutrition, spiritual development (self-actualization), interpersonal support, and stress management. The scale is graded in a 4-point Likert type as Never=1, Sometimes=2, Often=3, and Regularly=4. It does not contain any reverse expression. The total scores can range between 52 and 208 points. Sub-dimension scores are obtained by the total score of the answers given to the items in that sub-dimension; the sum of the subdimension scores obtains the total score. The higher scores indicate having better healthy lifestyle behaviors (11).

Statistical Analysis: Statistical analysis was performed using the Statistical Package for Social Sciences version 24 (IBM, Armonk, NY) software. Participants with missing values in an outcome variable were excluded from any analysis on that variable. Descriptive statistics were expressed as mean, standard deviation, minimum-maximum values, frequency, and percentile. Kolmogorow-smirnow test was used to determine the normal

distribution of the data set. Mann Whitney- U test, Kruskal Wallis tests were used to evaluate the relations between scores and socio-demographic characteristics of the participants. A p-value less than 0.05 was considered statistically significant with a 95% confidence level. Pearson correlation and Logistic regression analysis were used.

RESULTS

Of 524 participants, 305 (58.2%) were women. The mean age was 41.26±14.28 (min:18, max:75) years old. Of the participants, 45.2% had chronic disease, 32.1% were still smoking. The mean quantity of cigarettes smoked by 307 smokers and ex-smokers was calculated as 14.55±10.36 (min:1, max:50) pack/year. **Table 1** shows the socio-demographic characteristics of the participants.

Chronic diseases and tobacco use did not differ in both genders (p=0.859, p=0.266, respectively). Also, no difference was found between being diagnosed with COVID-19 and vaccinated against COVID-19 according to gender (p=0.854, p=0.261, respectively). Men's education level was higher **(p=0.027).** Marital status, income level, and changes in sleep patterns did not differ in both genders (p=0.311, p=127, p=0.877, respectively).

Table 1. The socio-demographic characteristics of the participants

	Number	**%**
Sex		
Female	305	58.2
Male	219	41.8
Marital Status		
Married	389	74.2
Single	135	25.8
Had a chronic disease		
Yes	237	45.2
No	287	54.8
Tobacco use		
Smoking	168	32.1
Not smoking	217	41.4
Quitted before the pandemic	91	17.4
Quitted during the pandemic	48	9.1
Education level		
Illiterate	20	3.8
Primary school	113	21.6
High school	183	34.9
University	183	34.9
Master degree	25	4.8
Economic status		
Income less than expenses	119	22.7
Income equal to expenses	279	53.3
Income more than expenses	126	24.0
Sleep changes		
Same sleep pattern	250	47.7
Increased sleep time	103	19.7
Decreased sleep time	94	17.9
Difficulty in falling asleep	77	14.7
Having a healthcare worker relative		
Yes	215	41.0
No	309	59.0
Having a relative who died due to COVID-19		
Yes	203	38.7
No	321	61.3
Infected with COVID-19		
Yes	187	35.7
No	337	64.3
COVID-19 vaccination status		
Vaccinated	349	66.6
Unvaccinated	175	33.4

Participants with chronic diseases significantly had more changes in their sleep pattern **(p=0.001).** While previous COVID-19 diagnosis had no significant impact on sleep pattern, those who had the COVID-19 vaccine had fewer sleep problems (p=0.882, **p=0.001).** Smoking, economic level, marital status did not affect sleep pattern (p=0.336, p=0.268, p=0.114). Those with higher educational status experienced fewer sleep pattern changes **(p=0.001).**

The mean total HPLS score was 162.75±8.10 points while the mean scores of the sub-dimensions were as follows: Taking responsibility for health: 29.38 ± 3.41, Physical activity: 20.05 ± 3.20, Nutrition: 28.94 ± 3.65, Spiritual development: 28.97 ± 3.64, Interpersonal relations: 30.37 ± 3.32, Stress management: 25.02 ± 3.95 points.

Interpersonal relationships, stress management, and total HPLS scores were higher in women **(p=0.030, p=0.001, p=0.005,** respectively**).** Stress management scores of singles were found to be statistically significantly higher **(p=0.001).** Physical activity, nutrition, stress management, and total scores were significantly higher in those without chronic diseases **(p=0.010, p=0.05, p=0.001, p=0.050,** respectively**).** The sub-dimensional scores of taking health responsibility were found to be higher in participants with chronic diseases **(p=0.003) (Table 2).**

Table 2. Health-promoting lifestyle scale (HPLS) scores of participants according to having at least one chronic disease

	Had Chronic Disease			
HPLS sub-dimensions	**Yes (Mean±SD)**	**No (Mean±SD)**	**Z**	**p**
Taking responsibility for health	29.89±3.44	28.97±3.33	-2.980	**0.003**
Physical activity	19.68±3.28	20.35±3.10	-2.563	**0.010**
Nutrition	28.63±3.58	29.20±3.70	-1.927	**0.050**
Spiritual development	28.79±3.61	29.11±3.67	-1.300	0.194
Interpersonal relations	30.59±3.22	30.18±3.40	-0.780	0.435
Stress management	24.35±3.94	25.58±3.88	-3.419	**0.001**
Total score	161.94±7.85	163.41±8.25	-1.904	**0.050**

SD: Standard Deviation

Participants who did not have COVID-19 disease diagnosis, had higher health responsibility and nutrition sub-dimensional scores **(p=0.001, p=0.008,** respectively**).** The interpersonal relations and stress management scores of the participants who recovered from COVID-19 disease were higher than those who never had the disease **(p=0.004, p=0.050,** respectively**) (Table 3).**

Table 3. Health-promoting lifestyle scale scores (HPLS) according to having COVID-19 diagnose

	Had the COVID-19 Disease?			
HPLS sub-dimensions	**Yes (Mean±SD)**	**No (Mean±SD)**	**Z**	**p**
Taking responsibility for health	28.54±3.50	29.85±3.27	-4.030	**0.001**
Physical activity	20.27±3.34	19.92±3.11	-1.708	0.088
Nutrition	28.37±3.72	29.26±3.58	-2.666	**0.008**
Spiritual development	28.96±3.29	28.97±3.83	-0.635	0.525
Interpersonal relations	30.95±3.04	30.04±3.43	-2.861	**0.004**
Stress management	25.45±4.07	24.78±3.87	-1.928	**0.050**
Total score	162.57±7.85	162.85±8.25	-0.358	0.720

SD: Standard Deviation

The sub-dimensional scores of health responsibility in those who had the COVID-19 vaccine were higher **(p=0.04)** while stress management scores were found to be higher in the unvaccinated ones **(p=0.020).** Having a healthcare worker relative had no effect on the total HPLS scores (p=0.833). Interpersonal relations scores of those who did not have a relative died because of COVID-19 disease were found higher **(p=0.004).** Health responsibility sub-dimensional scores of those who quitted smoking in the pandemic period were significantly higher **(p=0.001).** Physical activity scores of current smokers were lower **(p=0.008).** Nutrition and spiritual development (self-actualization) scores were higher in those who quitted smoking before the pandemic period **(p=0.050, p=0.001,** respectively**) (Table 4).**

Table 4. Comparison of tobacco use and the health-promoting lifestyle scale scores

	Tobacco use (mean±SD)					
HPLS sub-dimensions	**Smoking**	**Not smoking**	**Quitted before the pandemic**	**Quitted during the pandemic**	**χ^2**	**p**
Taking responsibility for health	29.13±3.44	29.26±3.44	29.24±3.22	31.10±3.08	16.185	**0.001**
Physical activity	19.51±2.86	20.53±3.38	19.62±3.05	20.56±3.41	11.787	**0.008**
Nutrition	28.86±3.84	29.16±3.32	29.35±3.59	27.45±4.21	7.548	**0.050**
Spiritual development	29.20±2.77	28.67±3.92	30.32±3.78	26.91±3.76	38.896	**0.001**
Interpersonal relations	30.37±3.46	30.62±3.32	29.75±3.27	30.37±2.84	5.114	0.164
Stress management	25.13±4.24	25.13±3.89	24.85±3.62	24.47±3.84	1.339	0.720
Total score	162.22±7.81	163.40±8.40	163.16±8.08	160.89±7.59	4.202	0.240

SD: Standard Deviation

The physical activity scores of those who did not have any changes in their sleep patterns were significantly higher **(p=0.007).** Spiritual development score was lower in those with increased sleep time during the pandemic period **(p=0.036).** Stress management score was found to be lower in those with decreased sleep duration during the pandemic period **(p=0.05) (Table 5).**

Table 5. Comparison of sleep pattern changes and the health-promoting lifestyle scale scores

	Sleep Pattern Changes (Mean±SD)					
HPLS sub-dimensions	**Same sleep pattern**	**Increased sleep time**	**Decreased sleep time**	**Difficulty falling asleep**	**χ^2**	**p**
Taking responsibility for health	29.38±3.30	29.05±3.47	29.87±3.27	29.25±3.83	2.370	0.499
Physical activity	20.51±3.30	19.75±2.77	19.46±3.43	19.66±2.93	12.000	**0.007**
Nutrition	28.84±3.73	29.33±3.10	28.81±3.98	29.20±3.55	0.602	0.896
Spiritual development	29.30±3.48	28.17±4.02	28.77±3.62	30.62±3.14	8.540	**0.036**
Interpersonal relations	30.19±3.36	30.68±3.53	30.28±3.16	25.79±4.35	2.438	0.487
Stress management	25.00±3.73	25.35±4.01	24.07±3.98	25.79±4.35	7.496	**0.050**
Total score	163.28±7.77	162.36±7.87	161.29±9.03	163.33±8.16	2.954	0.399

SD: Standard Deviation

Physical activity, mental development, and total scores were significantly higher in those with higher educated participants **(p=0.005, p=0.045, p=0.013,** respectively**).** Illiterate participants had higher interpersonal relations scores **(p=0.009).** Physical activity sub-dimension scores of those whose income was more than their expenses, were higher **(p=0.049).** Stress management and total scores of the participants whose income was less than their expenses during the pandemic period, were lower **(p=0.047, p=0.033,** respectively**).**

A weak positive correlation was found between the age of the participants and the sub-dimension scores of health responsibility **(r=0.133, p=0.003).** A weak negative correlation was found between age and physical activity sub-dimension scores **(r=-0.211, p=0.001).** In addition, a negative correlation was found between age and stress management sub-dimension score **(r=-0.125, p=0.004,).** Age did not correlate with other sub-dimensional scores and total scale score (p=0.396, p=0.589, p=0.080, p=0.057, respectively).

Logistic regression analysis was performed between age and health responsibility score **(R^2=0,018, p=0.002),** stress management score **(R^2=0,016, p=0.004),** and physical activity sub-dimension score **(R^2=0,045, p<0.001).** In the linear regression analysis, 4,5% of the decrease in the physical activity score is attributed to the increase in the age (R2 = 0.045) **(Fig1).**

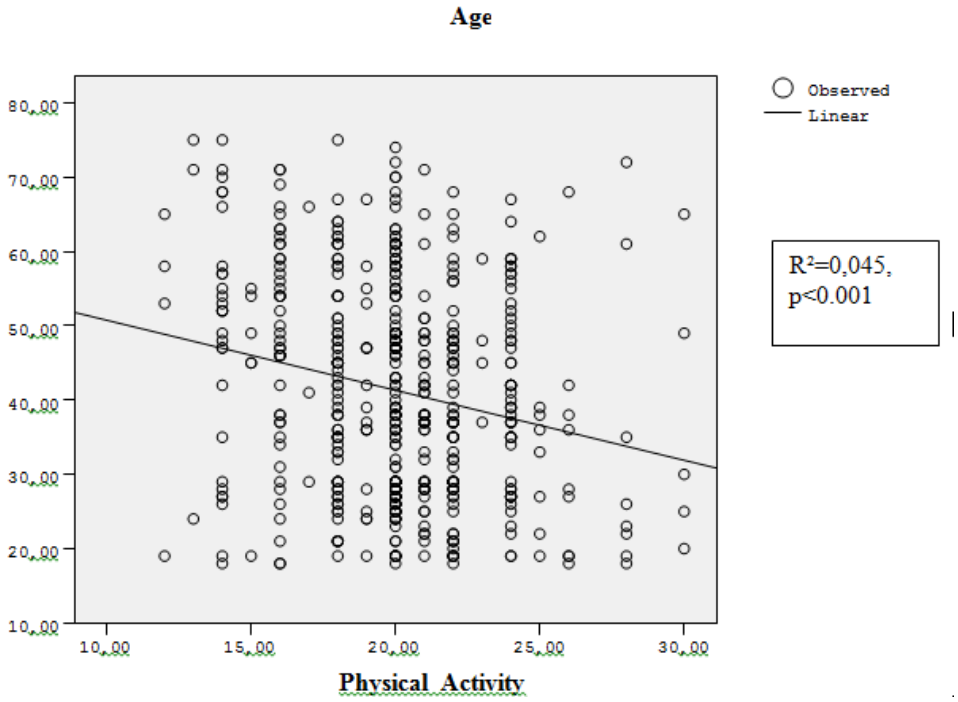

Figure 1. In the linear regression analysis between age and physical activity sub-dimension scores 4.5% of the decrease in the physical activity score is attributed to the increase in the age (R2 = 0.045).

DISCUSSION

In this study, health-promoting behaviors during the pandemic period were evaluated. The scores of women and those without chronic diseases were higher. Those who were infected with COVID-19 disease and those who had the COVID-19 vaccine had higher health responsibility sub-dimensional scores. Smokers' health responsibility and physical activity scores were low. Physical activity, mental development, and total scores of higher educated participants, were significantly higher.

It has been observed that most healthy behaviors are negatively affected during the pandemic period. It was stated that the participants were more stressed during their stay at home, they stayed away from social support, their sleep quality was impaired, and there was no difference in physical activity (12). Our study resulted in lower physical activity, interpersonal relationships, stress management sub-dimensional scores, and total HPLS scores. Physical activity scores were expected to be low since the prolongation of the closure period reduces outdoor activities. In addition, fighting an unexpected epidemic which has fatal consequences, can lead to uncertainty that negatively affects interpersonal relationships and difficulties in stress management.

In Spain, a study of 1254 adults proved that individuals with higher levels of social support, success in stress management, and more outdoor activities had higher healthy life behavior scores (7). In our study, interpersonal relationships, stress management scores and total HPLS scores were significantly higher in women than in men. In another study, women scored higher than men in terms of nutrition and anxiety levels while sleep quality satisfaction was higher in men (13). During the pandemic period, it was demonstrated that physical activity decreased, sedentary life increased, and the time spent in front of social media and television was prolonged (14). A decrease in average sleep duration and an increase in body weight were detected. Also, there was a decrease in fast-food consumption and an increase in the use of dietary supplement such as vitamin C, vitamin D, and zinc, during the social closure process. These nutrition changes were more pronounced in those who have had COVID-19 disease than others (14). In current study, nutrition scores were lower in those who had COVID-19 disease. Interpersonal relations scores of those who had a relative died from COVID-19 disease were low.

To protect and improve health during the pandemic period, the concept of health literacy should be well understood, and individuals should perceive the protection of their health as their own duty (15). In our study, the sub-dimensional scores of taking responsibility for health were higher in women, those with chronic diseases, those who quitted smoking in the pandemic period, and those who had COVID-19 vaccination and were not infected by COVID-19.

While no significant change was reported in participants' sleep habits during the pandemic, especially the sleep duration (13). According to another study the COVID-19 pandemic increased the prevalence of poor sleep quality in the population (16). Nearly half of the participants had disturbed sleep patterns and falling asleep problems in our study.

In a study, a significant percentage of participants reported that they were eating more frequently, larger amounts, and not making careful food choices (13). The low nutritional scores in our study indicate changing eating habits. These results support studies suggesting that overly stressed and anxious people tend to regulate their emotions through food (17).

Nursing students obtained the highest scores from the interpersonal relations and the lowest scores from the physical activity sub-dimensions. The vast majority of the participants got low scores in taking responsibility for health (18). In our study, taking health responsibility and interpersonal relationships scores were high, the physical activity score was similarly the lowest. In another study with healthcare professionals, the lowest score was found as physical activity (19).

We evaluated that the self-actualization scores were higher in those with a good education level. However, the interpersonal relations scores of the illiterate participants were higher. It can be interpreted as the lower educated participants were successful in keeping their relationships strong and healthy.

In previous studies, chronic kidney disease patients had the highest interpersonal relations scores and the lowest physical activity scores. The mean scores of male and married participants were found to be higher (20). The stress levels of diabetic patients increased, and their physical activities decreased during the pandemic period. A negative correlation was found between stress management and exercise scores (21). In the present study, while the health responsibility sub-dimensional scores of those with any chronic disease were higher, their nutrition scores and total HPLS scores were lower. Especially people over 65 years old and risky groups in oncology and cardiovascular diseases should be encouraged in healthy lifestyle behaviors (22).

Healthy lifestyle scores were lower among those who stated that they were in poor health, those who had a positive screening result for depression and anxiety, and those who had changes in nutrition and sleep (7). We found that the stress management scores of the participants who had the COVID-19 disease were high. Stress management must be successful for sustainable healthy living behaviors. Sleep quality and regular exercise can be

adversely affected by increased stress (23). In this study, the stress management scores of the participants who stated they had difficulty in falling asleep during the pandemic, were higher. Also, those with reduced sleep duration were more inactive in physical activities.

It was determined that non-smokers and those who quitted smoking had higher health responsibility, nutrition, interpersonal relations, and total scores than smokers. They were also able to implement healthy lifestyle behaviors better (24). In this study, those who quit smoking during the pandemic period had higher health responsibility scores. While the physical activity scores of active smokers were low, those who quitted smoking before the pandemic had higher spiritual development (self-actualization) scores. For people who cannot find the motivation to quit smoking, health concerns created by the pandemic period may have been the impetus to quit smoking. In addition, the high self-actualization scores of those who quitted smoking before the pandemic support the knowledge that self-control and stability are important in quitting smoking.

Our study has some limitations. The fact that the participation was voluntary may have resulted in more participation of those interested in healthy living. This may prevent generalizations from being made. In addition, since a self-evaluation scale used in the study, it is unknown whether the answers given are actual behaviors or socially desirable behaviors. However, the low scores obtained eliminate these possibilities. The fact that the study was conducted during the pandemic may have led to a decrease in the importance of healthy living behaviors because of other problems caused by the pandemic. Further studies conducted after the pandemic may yield beneficial results in evaluating the changes.

CONCLUSION

In conclusion, the scores obtained from the Healthy Lifestyle Behaviors Scale and its sub-dimensions were found to be low. Since health protection becomes essential in the pandemic period, studies that will contribute to the development of healthy lifestyle behaviors should be accelerated.

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RESEARCH ARTICLE

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The Effect of Different Doses of Amantadine on Lung Tissue in Hepatıc Ischemia Reperfusion Injury in Rats

ABSTRACT

Objective: N-Methyl D-Aspartate (NMDA) receptor blockers have been shown to have protective effects against ischemia/reperfusion (I/R) injury in various tissues. The aim of this study was to investigate the effects of 90 ve 135 mg/kg doses of amantadine on lung in hepatic I/R injury.

Methods: The rats were randomly divided into six groups: Group Sham, Group I/R, Group Amantadine-90, Group Amantadine-135, Group I/R-90 and Group I/R-135. In I/R, an atraumatic vascular clamp was applied to the structures in the left portal triad for 45 minutes and reperfusion period was 2 hours after ischemia. Malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) enzyme levels were performed the lung tissue and tissues were examined histopathologically.

Results: A significant difference was found between the groups in terms of MDA, SOD, CAT levels (respectively; $p < 0.001$, $p=0.008$, $p < 0.001$). A significant difference was found between the groups in terms of lung tissue neutrophil/lymphocyte infiltration scores and alveolar wall thickening scores (respectively $p=0.009$, $p=0.002$).

Conclusions: The biochemical and histopathological results of the present study suggested that amantadine, like other NMDA antagonist agents, may have a protective effect on lung tissues against the damage caused by hepatic I/R injury. Although we observed significant improvements after the administration of both doses studied, there was no significant difference between these two doses in terms of their success in protecting against distant organ lung injury. Amantadine appears promising as a therapeutic agent in treatment.

Keywords: Amantadine, Ischemia Reperfusion Injury, Lung Injury, Remote Organ Damage.

Sıçanlarda Hepatik İskemi Reperfüzyon Hasarında Farklı Dozlarda Amantadin'in Akciğer Dokusu Üzerine Etkisi

ÖZET

Amaç: N-Metil D-Aspartat (NMDA) reseptör blokerlerinin çeşitli dokularda iskemi/reperfüzyon (I/R) hasarına karşı koruyucu etkileri olduğu gösterilmiştir. Bu çalışmanın amacı, hepatik I/R hasarında 90 ve 135 mg/kg dozlarındaki amantadinin akciğer üzerindeki etkilerini araştırmaktır.

Gereç ve Yöntem: Sıçanlar her rastgele altı gruba ayrıldı: Grup Sham, Grup I/R, Grup Amantadin-90, Grup Amantadin-135, Grup I/R-90 ve Grup I/R-135. I/R'de sol portal triaddaki yapılara 45 dakika süre ile atravmatik vasküler klemp uygulandı ve iskemi sonrası 2 saat reperfüzyon uygulandı. Akciğer dokusunda malondialdehit (MDA), süperoksit dismutaz (SOD) ve katalaz (CAT) enzim düzeyleri ölçüldü ve dokular histopatolojik olarak incelendi.

Bulgular: MDA, SOD, CAT düzeyleri açısından gruplar arasında anlamlı fark bulundu (sırasıyla; $p < 0,001$, $p=0,008$, $p < 0,001$). Akciğer dokusu nötrofil/lenfosit infiltrasyon skorları ve alveolar duvar kalınlaşma skorları açısından gruplar arasında anlamlı fark bulundu (sırasıyla $p=0,009$, $p=0,002$).

Sonuç: Bu çalışmanın biyokimyasal ve histopatolojik sonuçları, hem 90 hem de 135 mg/kg dozdaki amantadinin, diğer NMDA antagonist ajanları gibi, karaciğer I/R hasarının neden olduğu hasara karşı akciğer dokuları üzerinde koruyucu bir etkiye sahip olabileceğini göstermiştir. Çalışılan her iki dozun uygulanmasından sonra önemli gelişmeler gözlememize rağmen, uzak organ akciğer hasarına karşı korumadaki başarıları açısından bu iki doz arasında anlamlı bir fark yoktu. Amantadin, tedavide terapötik bir ajan olarak umut verici görünmektedir.

Anahtar Kelimeler: Amantadin, İskemi Reperfüzyon Hasarı, Akciğer Hasarı, Uzak Organ Hasarı.

INTRODUCTION

Hepatic ischemia/reperfusion (I/R) injury is a major complication that can occur during liver surgeries, including operations such as liver resection, liver transplantation, and trauma surgery (1). Cellular disorder and organ dysfunction occur alongside the release of various mediators during tissue damage induced by blood deprivation (ischemia) and subsequent blood flow (reperfusion) (2). Further, I/R injury is one of the main underlying causes of post-transplant graft dysfunction (3).

Prolonged liver I/R causes hepatic cell damage and distant organ injury with high morbidity and mortality through the induction of reactive oxygen species (ROS) and pro-inflammatory cytokines (4,5). Damage to the lungs, kidneys, and heart from distant organs has also been shown to occur during liver I/R injury (6-8). Lung injury is an especially important cause of mortality in critically ill patients (8).

Amantadine is an N-methyl-D-aspartate (NMDA)-type glutamate receptor antagonist drug that was approved for use in the United States in 1968 and has been used in the treatment of both influenza and Parkinson's disease. While amantadine accomplishes its antiviral effect by preventing the release of viral RNA, it achieves its effects on the brain by increasing dopamine release, blocking dopamine reuptake, activating microglia, and inhibiting neuroinflammation. Amantadine has been reported to be effective in treating both acute and chronic phases of traumatic brain injury, and its use in different doses has been shown to have a neurorestorative effect on cerebral cortical ischemia (9).

Pharmacological agents that disrupt the reperfusion injury cascade constitute many of the preventative strategies currently under investigation to mitigate I/R injury (10). For example, NMDA receptor antagonist drugs (e.g., ketamine, barbiturates, volatile anesthetics, and morphine) have been previously shown to have protective effects against I/R damage in different tissues (e.g., kidney tissue, myocardium, and skeletal muscle) (11-13). However, no study in the literature has investigated the effects of amantadine on hepatic I/R injury. In our previous study of lower limb I/R, we administered 45 mg/kg amantadine and observed that it could reduce distant lung damage (14). In the present study, our aim was to investigate the protective effects of higher doses of amantadine (90 and 135 mg/kg) on lung tissue, which is a distant organ in hepatic I/R damage.

MATERIAL AND METHODS

This study, which was approved by the Sakarya University Animal Experiments Local Ethics Committee, was carried out at the Sakarya University Experimental Medicine Application and Research Center in January 2019.

Thirty-six adult male Wistar rats weighing 250–330 g were used in this study. These rats were adapted to the environment by being housed in a 12-hr-light:12-hr-dark environment until the beginning of the study. The subjects were examined in an environment of standardized light and temperature. Neither fluid nor feeding restrictions were applied to the animals, which received standard rat food (pellet feed). The weights of the rats were measured before anesthesia was administered, and their abdominal areas were shaved before the surgical incisions were made. All the rats were intraperitoneally (i.p.) to 100 mg/kg ketamine (Ketalar 1 ml: 50 mg, Pfizer, Istanbul, Turkey) and intramuscularly anesthetized injected with 15 mg/kg xylazine (Xylazine Bio 2%, Biovet, Czech Republic), intramuscularly administered 0.01 mg of atropine (Atropine Sulfate 0.5 mg/ml ampoule, Biofarma, Istanbul, Turkey). A heating blanket was used to prevent heat loss and hypothermia, and a rectal thermometer was used for temperature monitoring. The tail vein was cannulated with a 24-G IV cannula for drug administration and hydration.

Amantadine hydrochloride (Sigma A1260-5G) was purchased from Sigma-Aldrich (St. Louis, USA) and dissolved in sterile saline.

The rats were randomly divided into six groups: Group Sham (Group S, n = 6), Group I/R (n = 6), Group Amantadine-90 (Group A-90, n = 6), Group Amantadine-135 (Group A-135, n = 6), Group I/R-90 (n = 6), and Group I/R-135 (n = 6). After the anesthesia was applied, Groups S and I/R waited for 15 minutes without any action. In Groups A-90 and I/R-A-90, 90 mg/kg amantadine hydrochloride was administered with the anesthesia. Groups A 135 and I/R-A-135 were administered 135 mg/kg i.p amantadine. Then, Groups A-90, I/R-A-90, A-135, and I/R-A-135 waited for 15 minutes. In Groups S, A-90, and A-135, a middle abdominal incision was made on each rat but no intervention was applied to the liver. In Groups I/R, I/R-A-90, and I/R-A-135, a mid-abdominal incision was made on each rat to reveal the liver, the ligament attachments of the left lateral and median lobes were carefully separated, and the lobes were freed. The portal circulation of these lobes was separated, and an atraumatic vascular clamp was applied to the portal vein and the hepatic artery feeding the median and left lateral lobes (Figure 1). This procedure induced ischemia in approximately 65–70% of the liver. After 45 minutes of ischemia, the clamp was removed. Reperfusion was applied to the rats in Groups I/R, I/R-A-90, and I/R-A-135 for two hours.

All the rats were sacrificed after 180 minutes, and their lung tissues were obtained. The lung samples were kept at -80 °C for tissue homogenization and cut into small pieces on ice. These samples were weighed and placed in glass tubes, which were then filled with a cold phosphate buffer (pH 7.4, 50 mmol/L) to a final concentration of 100 mg tissue/mL. The homogenization process was carried out in a mechanical homogenizer

(Isolab, Laborgerate GmbH, Germany) on ice with an Isolab homogenization device. The resulting homogenate was centrifuged at 10,000 g and 4 °C for ten minutes and separated from debris and other extraneous particles.

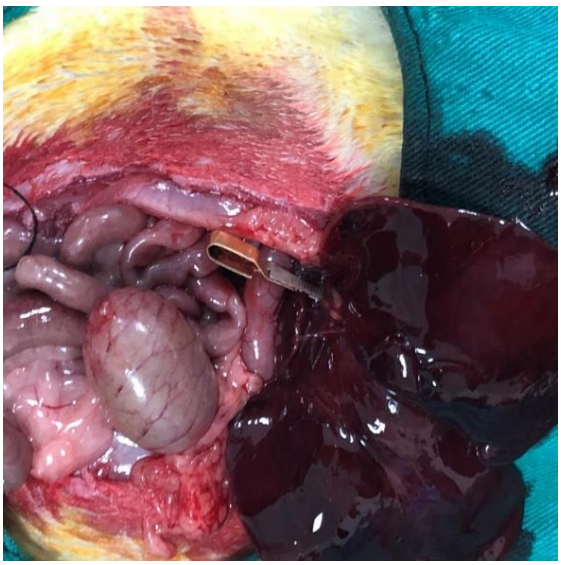

Figure 1. Liver dissection and clamping

All parameters were studied using the supernatants obtained after centrifugation. Catalase (CAT) and superoxide dismutase (SOD) levels were measured through an ELISA (Elabscience Biotechnology Co. Ltd., Wuhan, China). The within-measurement coefficient of variation (CV) of the kit was <10%, and the measurements were made in an automatic ELISA analyzer (Triturus, Grifols, Spain) in accordance with the manufacturer's protocols. The results were calculated by multiplying the obtained results by the dilution factor. Malondialdehyde (MDA) levels were measured and calculated using the same methods in order to determine lipid peroxidation status.

The lung tissue samples were stored in a 10% formaldehyde solution at +4 °C. Then, the tissues were stained with hematoxylin-eosin and evaluated with light microscopy in the laboratory of the Department of Histology and Embryology of the Sakarya University Faculty of Medicine. Ischemia was graded as Grade 0 (no sign of damage), Grade 1 (mild damage), Grade 2 (severe damage), or Grade 3 (severe damage) on the basis of neutrophil/lymphocyte infiltration and alveolar wall thickening scores.

Statistical Analysis: The data were transferred to the IBM SPSS Statistics 23 program for analysis. The study data for the numerical variables were represented as means ± standard deviations (SDs). A Kruskal Wallis test was used to check for differences between more than two groups, and differences between the groups were evaluated with a Mann-Whitney U test. A significance level of $p < 0.05$ was considered significant.

RESULTS

Lung tissue MDA, SOD, and CAT enzyme levels are shown in Table 1. A significant difference was found between the groups in terms of MDA levels ($p < 0.001$). A pairwise comparison of the groups revealed that the MDA levels of Groups A-90, A-135, I/R-A-90, and I/R-A-135 were significantly lower than those of Group I/R ($p = 0.002$, 0.002, 0.002, and 0.002, respectively). However, there was no significant difference between the MDA levels of Group I/R-A-90 and those of Group I/R-A-135 ($p = 0.485$).

Table 1. Oxidant status parameters of rat lung tissue

	Group S (n=6)	Group I/R (n=6)	Group A-90 (n=6)	Group I/R-A-90 (n=6)	Group A-135 (n=6)	Group I/R-A-135 (n=6)	p
MDA (nmol/100mg)	3.14±0.70	2.95±0.18	0.87±0.17*&	0.71±0.12*&	0.67±0.26*&	0.81±0.23*&	**<0.001**
SOD (ng/100mg)	3.75±1.02	3.13±1.33	1.72±0.37*&	1.62±0.27*&	1.69±0.85*&	1.95±0.97*&	**0.008**
CAT (ng/100mg)	4.54±0.84	4.37±1.24	22,81±2,84*&	22.25±1.83*&	22.24±6.03*&	22.02±5.98*&	**<0.001**

*Data are expressed as mean ± SD; *: p<0.05 versus Group I / R; &: p<0.05 versus Group S*

The groups also differed significantly in terms of lung tissue SOD levels ($p = 0.008$). A pairwise comparison of the groups revealed that the SOD levels of Groups A-90 and I/R-A-90 were significantly lower than those of Group I/R ($p = 0.041$ and 0.041, respectively). However, no significant difference was found between the SOD levels of Group I/R-A-90 and those of Group I/R-A-135 ($p = 1.0$).

A significant difference between the groups was also found in terms of CAT levels ($p < 0.001$). A pairwise comparison of the groups revealed that the CAT levels of Groups A-90, A-135, I/R A-90, and I/R-A-135 were significantly higher than those of Group I/R ($p = 0.002$, 0.002 0.002, and 0.002, respectively). No significant difference was found between the CAT levels of Group I/R-A-90 and those of Group I/R-A-135 ($p = 1.0$).

The neutrophil/lymphocyte infiltration and alveolar wall thickening scores determined through the histopathological examination of the lung tissues are shown in Table 2.

A significant difference was found between the groups in terms of lung tissue neutrophil/lymphocyte infiltration scores ($p = 0.009$). Specifically, neutrophil/lymphocyte infiltration was lowest in Group S and highest in Group I/R.

Table 2. Histopathological findings of rat lung tissue

	Group S (n=6)	Group I/R (n=6)	Group A-90 (n=6)	Group I/R-A-90 (n=6)	Group A-135 (n=6)	Group I/R-A-135 (n=6)	p
Neutrophil/lymphocyte infiltration	0.33±0.52	1.83±0.75[&]	1.50±0.55[&]	1.67±0.52[&]	1.50±0.55[&]	1.17±0.41[&]	**0.009**
Alveolar wall thickening	0.33±0.52	2.17±0.75[&]	1.50±0.55[&]	1.83±0.41[&]	1.17±0.41[&]	1.33±0.52[&]	**0.002**

Data are expressed as mean ± SD; &: p<0.05 versus Group S

Further, damage was decreased in Groups I/R-A-90 and I/R A-135 (Figure 2). Similarly, a statistically significant difference was found between the groups in terms of alveolar wall thickening scores (p = 0.002). Specifically, alveolar wall thickening scores were lowest in Group S and highest in Group I/R. Further, both alveolar wall thickening and neutrophil/lymphocyte infiltration scores were decreased in Groups I/RA-90 and I/R-A-135 (Figure 2). When the samples were examined with hemotoxylin eosin staining, capillary congestion, diffuse neutrophil infiltration, inflammation, and alveolar wall thickening were observed after I/R, whereas inflammation, alveolar wall thickness, and neutrophil infiltration were decreased after amantadine administration.

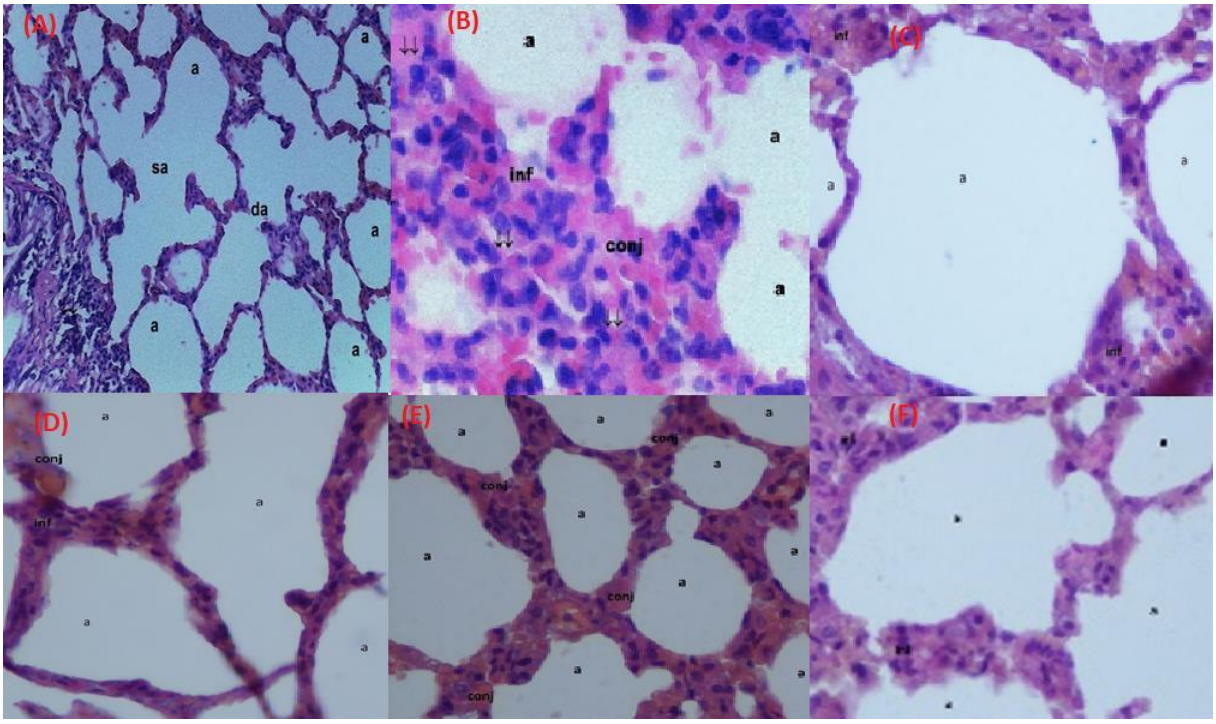

Figure 2. Lung tissue preparations, hematoxylin-eozin, X400: (A) Normal lung tissue parenchyma in Group S; (B). Capillary congestion, diffuse neutrophil infiltration, inflammation, alveolar wall thickening in Group I/R; (C) Inflammation and alveolar wall thickening in Group A-90; (D) Capillary congestion, neutrophil infiltration and alveolar wall thickening in Group-A-135; (E) Reduction on capillary congestion, neutrophil infiltration and alveolar wall thickening in Group I/R-A-90; (F) Reduction on inflammation and alveolar wall thickening in Group I/R-A-135. [s, saccus alveolaris; a, alveoli; d, ductus alveolaris; [↓↓, alveolar septum thickening; inf, inflamation; cong, conjugation]

DISCUSSION

The present study investigated the effects of 90 mg/kg and 135 mg/kg amantadine on lung tissues in a rat hepatic I/R model. The results showed that after I/R, a decrease in histopathological changes and changes in MDA, SOD, and CAT levels in lung tissues could limit lung damage.

Hepatic I/R injury is a complex process involving intrasignaling pathways, media, cells, and pathophysiological messages (15). The damage that develops as a result of this process is not limited to the liver, but causes a systemic response in the whole organism, especially lung and kidney (6-8). Previous studies on I/R injury have reported that NMDA receptor antagonists have protective effects against I/R damage in various organs and tissues (5,16). For example, Tufek et al. reported that administration of NMDA receptor antagonist dexmedetomidine before hepatic I/R injury caused decreases in total oxidant capacity and oxidative stress index as well as increases in total antioxidant capacity and PON-1 activity in the serum, liver, and distant organs (5). In another study, systemic injection of MK-801, an NMDA receptor antagonist, inhibited the activation of tumor necrosis factor-α (TNF-α), attenuated cell

infiltration and demyelination, and induced nitric oxide synthase and nitric oxide activity in a sciatic nerve I/R model. Further, it has been shown to reduce and thus protect against I/R damage (17). Another study reported that in intestinal I/R injury, serum aspartate aminotransferase, lactat dehydrogenase, TNF-α, MDA, and P-selectin levels increased while angiotensin III levels and total antioxidant capacity decreased and severe damage was observed in the intestinal mucosa; however, these changes were significantly improved with ketamine administration (16).

The compound MDA is the end product of lipid peroxidation. An increase in MDA levels is an indicator of free radical formation in postischemic tissue (18), as an increase in free radicals causes MDA to be overproduced. Increased MDA has been found to be associated with hepatic I/R damage and is widely used to determine I/R damage (19,20). Sahin et al. showed that the MDA levels of liver tissues increased after hepatic I/R and decreased with dexmetomidine administration (19). In another study, MDA levels increased after hepatic I/R but decreased with melatonin administration (20). Similar to other studies in the literature, the present study showed that the MDA levels of lung tissues increased after I/R injury and decreased with amantadine administration. However, we did not find any significant differences between 90 mg/kg and 135 mg/kg amantadine administration.

The enzymes SOD and CAT are responsible for cellular antioxidant defense mechanisms. These enzymes remove superoxide anions and hydrogen peroxide (H2O2) and prevent free radical production. The SOD enzyme is the primary defense mechanism against free oxygen radicals and catalyzes the conversion of H2O2- to O2- (21). There are two common opinions in the literature regarding SOD. On one hand, the SOD activity levels of tissue and serum samples have been shown to decrease after I/R damage, in comparison with control groups, due to the dominance of oxidant mechanisms and increased with antioxidant administration (19). In another opinion, it is thought that SOD activity increases with I/R damage to control oxidative stress. One study supporting this latter view showed that SOD levels increased after I/R but decreased with dexmetomidine administration (22). Another study showed that the SOD levels of lung tissues increased with I/R (23). In line with this view, we observed in the present study that SOD levels increased after I/R injury but decreased with the application of amantadine. While SOD levels decreased with the application of both doses (90 mg/kg and 135 mg/kg) of amantadine, we observed a more significant decrease in the group that was administered 90 mg/kg amantadine.

Oxidoreductases, another group of antioxidant enzymes, are among the most important free radical scavenging systems and play a cell protective role. The CAT enzyme is one of these antioxidant enzymes. The CAT enzyme catalyzes H_2O_2 destruction, and high blood levels of CAT indicate antioxidant activity. Kucuk et al. showed that CAT levels decreased after hepatic I/R and increased with the application of dexmetomidine, an NMDA receptor antagonist (22). In another study, CAT levels decreased after hepatic I/R and increased with the administration of different doses of dexmetomidine [19]. As in these other studies, the present study showed that CAT levels decreased after I/R and increased significantly with the application of amantadine in both examined doses (90 mg/kg and 135 mg/kg). However, no differences were observed between these doses.

The lungs are among the organs most affected by distant organ damage during I/R (24-25). Perivascular and peribronchial edema, increases in alveolar wall thickness, and leukocyte infiltration have been observed in lung tissues after hepatic I/R (26). Similarly, another study reported that necrosis, inflammatory cells, bleeding, and microsteatosis significantly increased in the lungs after hepatic I/R injury (27). In the present study, increases in alveolar wall thickness and neutrophil/lymphocyte infiltration rates were observed after I/R, while these symptoms significantly decreased with amantadine treatment. Although the patients who received 135 mg/kg amantadine experienced a greater decrease in these symptoms than those who received 90 mg/kg amantadine, this difference was not significant.

CONCLUSION

The biochemical and histopathological results of the present study suggested that amantadine, like other NMDA antagonist agents, may have a protective effect on lung tissues against the damage caused by hepatic I/R injury. Although we observed significant improvements after the administration of both doses studied, there was no significant difference between these two doses in terms of their success in protecting against distant organ lung injury. Amantadine appears promising as a therapeutic agent in treatment.

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RESEARCH ARTICLE

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Investigation of Serum Folate-Receptor-1 in Patients with Non-Small Cell Lung Cancer

ABSTRACT

Objective: Histopathological overexpression of folate receptor-1(FOLR1) involved in folate transport in cell growth has been reported in various cancers. Increased serum FOLR1 (sFOLR1) has also been reported in epithelial ovarian cancer. The aim was to investigate sFOLR1 levels in non-small cell lung cancer(NSCLC) patients and the response prediction of the standard chemotherapy targeting folic acid metabolism.

Methods: In this prospective study, sFOLR1 levels were investigated in 30 healthy individuals and 60 patients with stage4 malign metastatic NSCLC before and after standard chemotherapy. The commercial immunoassay(ELISA) kit was used for the analysis of sFOLR1. Serum carcinoembryonic antigen(CEA), vitamin B12, and folate levels were also investigated.

Results: In NSCLC patients sFOLR1 levels were significantly higher($p<0.001$) than the healthy individuals. After 3 months of standard treatment, sFOLR1 was significantly lower than pre-treatment values in NSCLC patients($p<0.001$). Diagnostic accuracy was strong in the differentiation of NSCLC patients from healthy individuals(AUC= 0.966). with the cut-off point of 82.45 pg/ml, the sFOLR1 level was performed with 95% sensitivity and 99% specificity. Pretreatment sFOLR1 levels were significantly lower in patients with-response to standard chemotherapy($p<0.01$). The best predictive value was determined as 393.80 pg/ml. At the end of the 401 days, a significant difference was found in patients with high sFOLR1 predictive value. The median overall survival(OS) duration was 288 days for all patients (95% GA 198.13-377.87). Median progression-free survival(PFS) was 321 days(95% GA 211.90-430.10).

Conclusions: For monitoring standard chemotherapy with drugs targeting folic acid metabolism, sFOLR-1 levels may be an important biomarker.

Keywords: Folate receptor 1 (FOLR1), Carcinoembryonic Antigen (CEA), Non-Small Cell Lung Cancer (NSCLC), Chemotherapy, Biomarker.

Küçük Hücreli Dışı Akciğer Kanserli Hastalarda Serum Folat-Reseptör-1 Düzeylerinin Araştırılması

ÖZET

Amaç: Hücre büyümesinde folat taşınmasında rol oynayan folat reseptörü-1'in (FOLR1) histopatolojik aşırı ekspresyonu çeşitli kanserlerde bildirilmiştir. Artmış serum FOLR1(sFOLR1) epitelyal yumurtalık kanserinde de rapor edilmiştir. Amaç, küçük hücreli dışı akciğer kanseri (KHDAK) hastalarında sFOLR1 düzeylerini ve folik asit metabolizmasını hedefleyen standart kemoterapinin tahminini yanıtını araştırmaktı.

Gereç ve Yöntem: Bu prospektif çalışmada, standart kemoterapi öncesi ve sonrası evre4 malign metastatik KHDAK'li 60 hasta ve 30 sağlıklı bireyde sFOLR1 düzeyleri araştırıldı. Ticari immünolojik test (ELISA) kiti sFOLR1'in analizi için kullanıldı. Serum karsinoembriyonik antijen (CEA), vitamin B12 ve folat düzeyleri de araştırıldı.

Bulgular: KHDAK hastalarında sFOLR1 seviyeleri sağlıklı bireylere göre anlamlı derecede yüksekti($p<0,001$). 3 aylık standart tedaviden sonra hastalarda sFOLR1 anlamlı olarak daha düşüktü ($p<0,001$). KHDAK hastalarının sağlıklı bireylerden ayırt edilmesinde tanısal doğruluk güçlüydü (AUC= 0.966). Tanısal doğruluk sFOLR1 seviyesi 82.45 pg/ml kesme noktasında %95 duyarlılık ve %99 özgüllük gerçekleştirmiştir. Standart kemoterapiye yanıt veren hastalarda tedavi öncesi sFOLR1 düzeyleri anlamlı olarak daha düşüktü($p<0.01$). En iyi tahmin değeri 393.80 pg/ml olarak belirlendi. 401 günün sonunda sFOLR1 tahmin değeri yüksek olan hastalarda anlamlı fark bulundu. Medyan genel sağkalım (OS) süresi tüm hastalar için 288 gündü (%95 GA 198.13-377.87). Medyan progresyonsuz sağkalım (PFS) 321 gündü (%95 GA 211.90-430.10).

Sonuç: Folik asit metabolizmasını hedefleyen ilaçlarla standart kemoterapiyi izlemek için sFOLR-1 seviyeleri önemli bir biyobelirteç olabilir.

Anahtar Kelimeler: Folat Reseptörü 1 (FOLR1), Karsinoembriyonik Antijen (CEA), Küçük Hücreli Olmayan Akciğer Kanseri (KHDAK), Kemoterapi, Biyobelirteç.

INTRODUCTION

The most common cause of cancer-related death is lung cancer (LC) (1) and approximately 80% of LCs are NSCLC (2). Although molecular targeted treatment research is intensive, chemotherapy is still a treatment option for patients with advanced NSCLC (3). Platinum-based doublet, usually cisplatin or carboplatin, is the standard treatment for advanced NSCLC (4).

Folate receptor-1 is a glycosylphosphatidylinositol-associated glycoprotein binding to folic acid and its derivatives with strong affinity. FOLR1 mediates the transport of folate through receptor-mediated endocytosis. Histopathological overexpressed FOLR1 in various solid tumors such as breast, ovarian, pancreatic, kidney, and lung cancer, especially NSCLC and high-grade osteosarcoma, was caused by the increased metabolic needs of folates to feed nucleic acid synthesis and cellular growth (5–11). FOLR1 could be transferred from the localized cell surface to the bloodstream as a soluble form of sFOLR1(12,13). In patients with malignant epithelial ovarian cancers to distinguish them from benign patients and healthy subjects, sFOLR1 has been reported as a potential biomarker (6).

Biomarkers for differential diagnosis, prognosis, or follow-up of lung cancer are quite limited. The expression of CEA in pulmonary adenocarcinoma and lymph node metastasis was higher than in other types of NSCLC (14). Therefore, only CEA levels were used to detect the efficacy of chemotherapy and early relapses in NSCLC. Nevertheless, CEA was not effective in identifying an early-stage disease or differential diagnosis (14).

There is a need for good predictive markers for the clinic evaluation of NSCLC. It would be useful to define laboratory tests for diagnosis and prognosis. The purpose of our study was to define sFOLR1 levels and evaluate its use in follow-up of NSCLC patients.

MATERIAL AND METHODS

Sixty (60) patients with metastatic stage4 NSCLC and 30 healthy individuals as a control group were included in this prospective study at the medical oncology clinic of the tertiary research hospital. The local institutional review board approved the project and this study conformed to the provisions of the 1995 Helsinki Declaration. All participants provided written informed consent before sample collection. This study adheres to the REMARK guidelines (15,16).

Demographic characteristics of participants (age, gender, height, weight, smoking, alcohol, diabetes mellitus, hypertension) were investigated (Table 1). Standard chemotherapy could be a choice in metastases such as bone or liver of NSCLC. Combinations of doublet chemotherapy drugs such as cisplatin, carboplatin, paclitaxel, etoposide, and pemetrexed or with a single chemotherapy drug to treat especially for people with poor overall health or who cannot tolerate combination chemotherapy well, such as the elderly could often constitute (17).

Table 1. Characteristics of study participants.

	Healthy (n:30) Mean ±SD/ Median (min-max)	**NSCLC patients Pre-treatment (n:60)** Mean ±SD/ median (min-max)	**NSCLC patients Post-treatment(n:60)** Mean ±SD/ median (min-max)
Demographic Data	**n (%)**	**n (%)**	
Smoking (current)	0	50 (83.3%)	
Drinking (current)	0	20 (33.5%)	
Diabetes mellitus	0	12 (20%)	
Hypertension	0	25 (41.6%)	
Age(year)	57.3±12.06	60.38±6.28 (p=0.295)	
BMI	26.94 ±0.64	25.46 ±0.43 (p=0.210)	
Laboratory data			
Vitamin B12 (pg/mL)	502.8(348-687)	**383.36 (103.2-893)[a]**	
Folate (ng/mL)	13.65(5.9-19.6)	**3.24(1.3-6.98)[a]**	
CEA (ng/mL)	1.71(1.2-2.81)	**15.59 (1.07-105.9)[a]**	**12.32(1.04-77.91)[b]**
sFOLR1 (pg/mL)	230.50(203.5-346.0)	**518.95 (206.18-1342)[a]**	**325.04(195.2-838.13)[b]**

Statistically significant p values are marked in **bold**. a: between healthy and NSCLC; **b:** between pre-treatment and post-treatment.
BMI: Body mass index; CEA: Carcinoembryonic Antigen; sFOLR1: serum Folate Receptor-1; SD: standard deviation; min: minimum; max: maximum

The response was evaluated with modified Response Evaluation Criteria in Solid Tumors (mRECIST) (18) in all patients with NSCLC three months after standard chemotherapy. The largest diameter measured in primary tumors and the shortest diameter measured in metastatic lymph nodes were evaluated. After treatment, the change in the size of the primary tumor was evaluated for the response. Lesions were grouped into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (18,19). According to the treatment response of lesions, patients have been grouped as " with-response" and "without-response"(18). "With-response" patients had lesions with CR and PR, and "without-response" patients had stable (SD) and progressive (PD) lesions.

Laboratory Assessments: Peripheric venous blood samples were collected from patients before treatment and three months after standard

chemotherapy (usually 80 mg/m2 cisplatin). After centrifugation at 3000 rpm for 10 minutes, the sera were stored at -80 ° C until the analysis. CEA, vitamin B12, and folate levels were examined by immunofluorescent method with Cobas e601 analyzer (Roche diagnostics; Geneva, Switzerland). sFOLR1 levels were analyzed with Sun Red Biotechnology Company's Human FOLR1 Elisa kit (Catalog No: SRB-T-87946).

Statistical Assessments: The Kolmogorov-Smirnov test was applied to all groups and the parametric/non-parametric distribution of parameters was figured out. The difference between groups in parameters; student t-test for parametric distribution and Mann-Whitney U for non-parametric distribution were performed. Correlation analysis and the relationships between parameters were evaluated. All statistical analyses were performed with SPSS22.0 (SPSS Inc., Chicago, IL) program and p values less than 0.05 were considered statistically significant. Optimal cut-off and area under the curve (AUC) levels for serum FOLR1 and CEA were figured out using the receiving operator characteristics curve (ROC), for the difference between healthy and NSCLC patient groups and between with-response and without-response groups. At the end of the follow-up period, OS and PFS of higher or lower than cut-off values groups were evaluated with Kaplan Meier analysis.

RESULTS

Demographic data of NSCLC patients and healthy individuals were presented in Table 1. All subjects were male and the age and body mass index (BMI) of patients with metastatic NSCLC were like healthy subjects (p=0.295, p=0.210, respectively). Serum vitamin B12 and folate levels were significantly lower in the patient group (both, p<0.001). Serum CEA and FOLR1 levels were significantly higher in patients (both, p<0.001). After 3 months of treatment in the patient group, serum CEA and FOLR1 levels were significantly lower than pre-treatment levels (both, p<0.001) (Table 1).

The efficacy of CEA and sFOLR1 levels in the separation of NSCLC patients from healthy examined with ROC analysis. The diagnostic competence of both CEA (AUC= 0.949) and sFOLR1 (AUC= 0.966) was strong (AUC>70.0) with 90% sensitivity and 90% specificity for CEA, and 95% sensitivity and 99% specificity for FOLR1. Optimal cut-off values (CEA= 2.11 ng/ml and sFOLR1=282.45 pg/ml) were determined for the difference between patients with NSCLC and healthy groups (Table 2).

Table 2. Area under the curve of parameters at diagnosis and after treatment.

Test Result Variable(s)	Cut-off	Area Under Curve (AUC)	Asymptotic Significance	Asymptotic 95% Confidence Interval		Sensitivity (%)	Spesificity (%)
				Lower Bound	Upper Bound		
CEA1	2,11	0,949	**<0,001**	0,895	1,000	90	90
sFOLR1 (pre-treatment)	282,4	0,966	**<0,001**	0,919	1,000	95	99
sFOLR1 (post-treatment)	393.8	0.870	**<0,001**	0.762	0.977	79	67

According to the standard chemotherapy response, patients were grouped as "with-response" and "without-response". The six patients in the with-response group were CR and the other ten were in the PR group. In the without-response group, twelve patients were SD and the other twelve were PD (Figure 1) with mRECIST criteria. There was no significant difference in pre-treatment CEA levels between the with-response and the without-response groups (p>0.05). On the other hand, pre-treatment sFOLR1 levels were significantly lower in patients with-response than without-response group patients (p<0.01) (Figure 1). The best predictive value was decided as 393.80 pg/ml with 79% sensitivity and 67% specificity in ROC analysis (Figure 2).

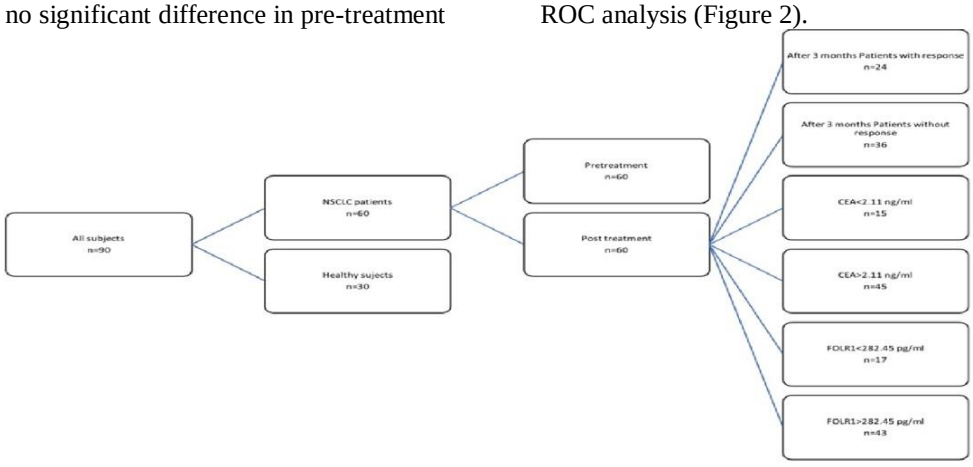

Figure 1. Participants in study groups

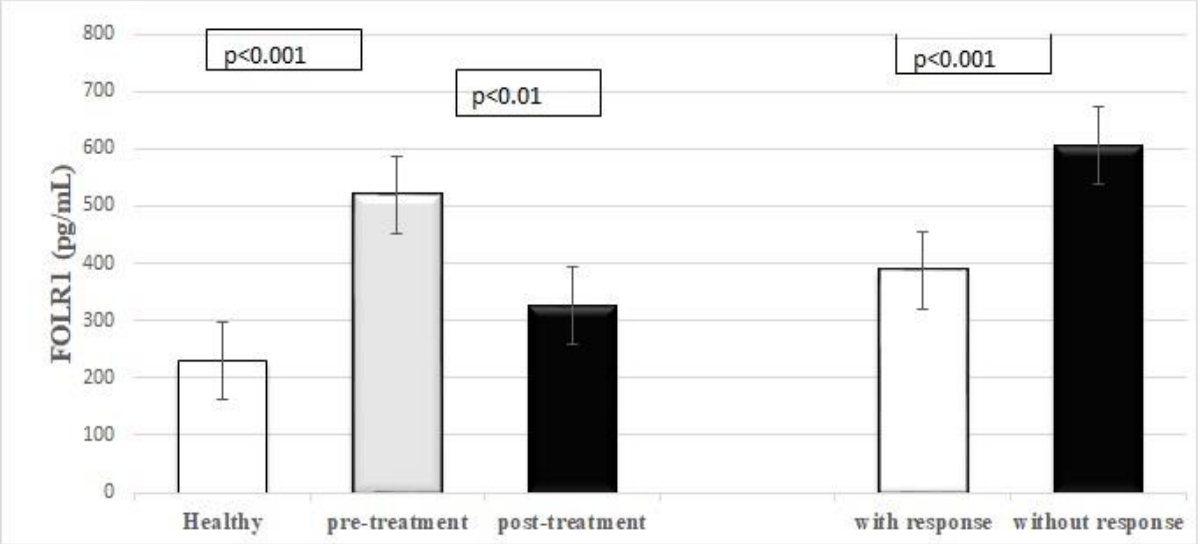

Figure 2. Serum FOLR1 levels of groups.

The average follow-up time was 401 days (range 91-452 days). At the end of the follow-up period, OS and PFS were evaluated with Kaplan-Meier analysis. A significant difference was detected in terms of OS and PFS in patients with pre-treatment FOLR1 levels above the predictive cut-off value. High sFOLR1(≥393.80 pg/ml) levels predicted significantly poor response than low sFOLR1 (<393.80 pg/ml) levels (Figure 3). Those with low sFOLR1 levels (<393.80 pg/ml) predicted good response than those with high (≥393.80 pg/ml) levels. Median OS time was 288 days (95% GA 198.13-377.87) and PFS was 321 days (95% GA 211.90-430.10).

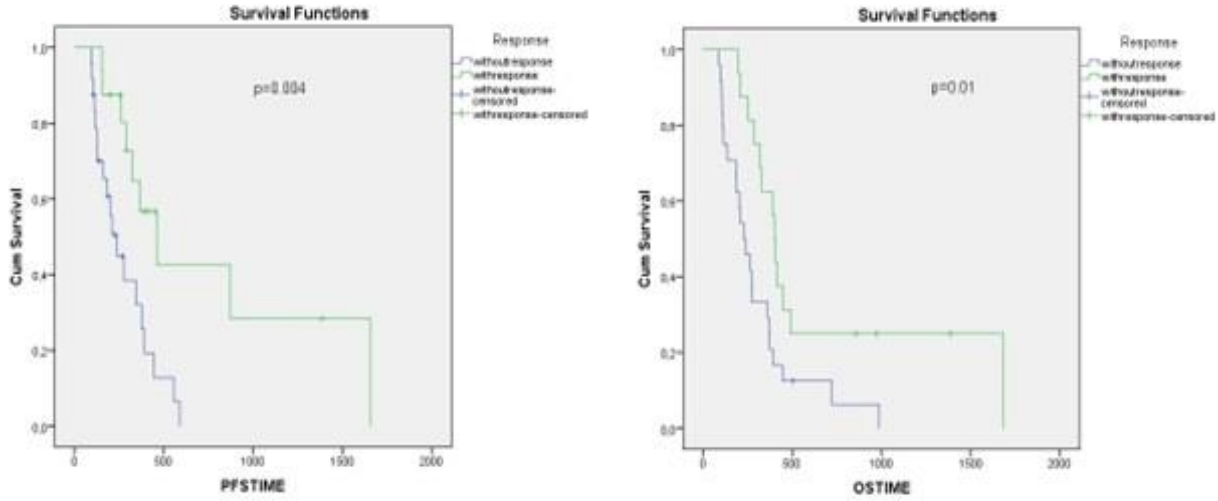

Figure 3. Progression free survival (PFS) and overall survival (OS) of with response and without response groups.

DISCUSSION

Histopathological FOLR1 (FRα gene) mRNA expression has been reported to be significantly higher in cancers such as mesothelioma, lung, pancreas, ovarian, and colorectal cancers (8–11). Over-expression histopathological FRα has been reported in adenocarcinoma compared to squamous cell cancers (7,20). Similarly, membrane carrier FOLR1 and reduced folate carrier-1 proteins were often reported overexpressed in NSCLC patients (3,21). However, there has been no study evaluating the role of sFOLR1 levels as a potential biomarker for lung cancers. In our study, sFOLR1 levels were significantly higher in NSCLC patients than in healthy individuals (Table 1). This result is consistent with the expression results reported in other studies and this study is the first study reporting serum levels. Although there are no studies on sFOLR1 levels in NSCLC; It has been reported as a biomarker for ovarian cancer and has been reported to be significantly higher than healthy controls (12,22). This supports our results in terms

of serum FOLR1 levels that could be used as tumor markers. Therefore, an easy-to-obtain and fast-achievable marker such as serum can provide a great advantage in the follow-up of patients.

Diagnostic efficacy and AUC values were remarkably high in ROC analysis, which evaluated the diagnostic effectiveness of sFOLR1 levels in the patient group (AUC= 0.966). At the highest level of sensitivity and specificity, the optimal cut-off value was 282.45 ng/ml.

On the other hand, CEA has been routinely used as a serum biomarker of lung cancer follow-up. High false-positive rates have been reported in lung cancer due to their low specificity for CEA levels, screening, or early diagnosis followed by traditional markers (12). However, it has proven to be a poor diagnostic indicator of sensitivity and specificity for LC. Thus, additional biomarkers are needed. In this study, the AUC value for CEA(AUC=0.949) was lower than sFOLR1. Therefore, sFOLR1 was a potential candidate to compensate for a lack of biomarkers needed in LC. To support our findings, sFOLR1 levels showed higher specificity and higher sensitivity than CA125 in the detection of epithelial ovarian cancer based on ROC analysis (6). A combined analysis of CEA and sFOLR1 may be useful for the early diagnosis and the treatment response of NSCLC. Additionally, such a combination could improve specificity and prediction of treatment efficacy.

In this study, sFOLR1 levels were significantly decreased 3 months after standard chemotherapy (Table 1). Over the past decades, FOLR1 has attracted much attention in antitumor therapy (23). Like our findings, in ovarian cancer cells, high expression of FOLR1 levels has been reported as a useful therapeutic application to increase sensitivity to cisplatin treatment (23), and reported also that FOLR1 was highly expressed in ovarian cancer but was reduced following multidrug resistance (23). At the same time, FOLR1 has been reported as a potential target for evaluating the response to treatment of human carcinomas with pemetrexed, a thymidylate synthase (TS) inhibitor (24). There have been reports that FOLR1 was highly expressed in NSCLC (3) and FOLR1 expression was associated with the prognosis of patients with NSCLC (21,25). However, to our knowledge, few studies were performed to explore the association between FOLR1 expression and drug resistance in NSCLC. The data we provide here that recommend, sFOLR1 levels were a key marker in monitoring standard chemotherapy treatment of NSCLC. When the patient groups' response to chemotherapy treatment was examined: there was no significant difference in pre-treatment CEA levels between the with-response and without-response groups, while pre-treatment sFOLR1 levels were significantly lower in patients with-response (Figure 1). According to the ROC analysis, in determining patients' good response to treatment: those with sFOLR1 levels below 393.80 pg/ml were the better response.

All patients were monitored for 401 days to assess survival and a significant difference was detected in terms of OS and PFS in patients with above sFOLR1 predictive value. Survival time decreased in those with sFOLR1 levels above 393.80 pg/ml. To support our findings, Kurosaki et al. high sFOLR1 levels in epithelial ovarian tumors predicted shorter PFS (6,24). Similarly, O'Shannessy, et al. (2012) reported shortened survival of those with high histopathological FOLR1 overexpression in patients with pulmonary adenocarcinoma (25). Combined detection of CEA and sFOLR1 may be useful for the early diagnosis and the treatment response of NSCLC. Additionally, such a combination could improve specificity and treatment prediction.

Our study should be interpreted with its limitations. The small sample size was the major limitation. The uncertainty of the factors affecting sFOLR1 levels, and to the best of our knowledge the lack of studies on serum levels in NSCLC patient groups were other limitations. However, the data we provide here suggest that FOLR1 may be a useful predictive biomarker for NSCLC. The results obtained in the NSCLC patients would be valuable for the potential role of sFOLR1 as a candidate biomarker. Our findings on FOLR1 are an important addition to the literature in this field. Further research is warranted to develop better prediction tools in NSCLC.

CONCLUSION

Serum FOLR1 levels were significantly higher in NSCLC patients than in the healthy subjects. Serum FOLR1 levels were significantly lower in patients with-response to standard treatment, and OS and PFS durations were significantly longer in those pretreatment sFOLR1 levels under 393.80 pg/ml. As a result, sFOLR1 levels appear to be a potential biomarker candidate in NCSLC patients' predicting the response to treatment. It will be appropriate to support our findings with data from larger samples.

Clinical Trial Number: 2018.110.08.01 of the Relevant Ethics Committee

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Conflict of Interest: None to declare.

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RESEARCH ARTICLE

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Health Literacy Assessment Tool related to Antenatal Care (HLAT-ANC) for Pregnant Women: A Methodological Research from Turkey

ABSTRACT

Objective: It is important to provide adequate antenatal care (ANC) for the lowest maternal-fetal complications in pregnancy. The increase in the level of health literacy increases the quality of the ANC, compliance with the follow-up. To develop a tool to evaluate health literacy (HL) levels of pregnant women in antenatal care (ANC).

Methods: This study is methodological research conducted between 15.02.2016-01.07.2018. "Health Literacy Assessment Tool related to Antenatal Care (HLAT-ANC)" was developed. Its validity-reliability was tested by item analysis, exploratory factor analysis (EFA), concurrent criterion validity, intergroup dissociation, and confirmatory factor analysis (CFA), and determination of the Kuder-Richardson-20 (KR-20) coefficient.

Results: The discrimination coefficients of the items in HLAT-ANC varied between 0.20-0.57 and factor loads between 0.34-0.85. It was determined that HLAT-ANC has KR-20≥0.85 in each subdomain. The scores of fit criteria obtained in the confirmatory factor analysis were within acceptable limits.

Conclusions: HLAT-ANC was found to be a valid and reliable scale.

Keywords: Health Literacy, Antenatal Care, Pregnancy, Methodological Research.

Gebelerin Doğum Öncesi Bakım İle İlgili Sağlık Okuryazarlık Düzeylerini Değerlendirme Aracının Geliştirmesi: Metadolojik Bir Çalışma, Türkiye

ÖZET

Amaç: Gebelikte maternal-fetal komplikasyonları en aza indirmek için yeterli doğum öncesi bakım (DÖB) alınması önemlidir. Sağlık okuryazarlık (SOY) düzeyinin yükseltilmesi, DÖB'nin kalitesini ve takibe uyumu arttırmaktadır. Bu çalışmada gebelerin DÖB ile ilgili SOY düzeylerini değerlendirme aracının geliştirilmesi amaçlandı.

Gereç ve Yöntem: Bu çalışma 15.02.2016-01.07.2018 tarihleri arasında gerçekleştirilen metadolojik bir araştırmadır. Doğum Öncesi Bakıma İlişkin Sağlık Okuryazarlığı Değerlendirme Aracı (DÖB-SOY)" geliştirildi. Geçerlik ve güvenirlik için, madde analizi, açımlayıcı faktör analizi (AFA), eşzamanlı ölçüt geçerliliği, gruplar arası ayrışma, doğrulayıcı faktör analizi (DFA) ve Kuder-Richardson-20 (KR-20) katsayısı hesaplandı.

Bulgular: DÖB-SOY'un maddelerinin ayırt edicilik katsayıları 0.20-0.57 arasında, faktör yükleri 0.34-0.85 arasında değişmektedir. KR-20, herbir alt alanda ≥0.85 olarak hesaplandı. Doğrulayıcı faktör analizinde elde edilen uyum kriterlerinin puanları kabul edilebilir sınırlar içindedir.

Sonuç: DÖB-SOY geçerli ve güvenilir bir ölçüm aracıdır.

Anahtar Kelimeler: Sağlık Okuryazarlığı, Doğum Öncesi Bakım, Gebelik, Metadolojik Çalışma.

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INTRODUCTION

The definition of "Maternal Health Literacy (MHL)" has been developed in order to adapt the generally used health literacy (HL) concept to the results of health education regarding mother and child health. Maternal health literacy is defined as "cognitive and social skills defined as the motivation and ability of women to access, understand and use health-related information in order to protect and improve themselves and their children's health"(1). The main purpose of maternal health literacy is to prepare women to make and manage decisions about their children's health during pregnancy and the postpartum period. The level of MHL is increased with antenatal education focused on developing skills related to pregnancy, birth, and infant care. Since the HL level of many pregnant women is low, they do not understand the importance of prenatal care and therefore face adverse pregnancy outcomes (2).

This study's aim was to develop a tool to evaluate health HL levels of pregnant women in ANC.

MATERIAL AND METHODS

This study is a methodological study conducted on pregnant women living in Eskisehir (a province of Western Turkey) between 15.02.2016-01.07.2018 with the aim of developing the Health Literacy Assessment Tool related to Antenatal Care (HLAT-ANC).

In order to develop HLAT-ANC, HL scales, which are widely used in research, were examined first. It was observed that these scales could not evaluate the HL level in relation to the prenatal period due to reasons such as containing items not suitable for Turkish cultural structure, having translation problems, not wanting to deteriorate the original structure of the scales. Additionally, these scales aim to measure of the General HL level. Therefore, it was decided to develop HLAT-ANC. For this purpose, a comprehensive literature review was performed first. A question pool consisting of 130 items was created based on the Test of Functional Literacy in Adults (TOFHLA), which is widely used in research.

The educational materials prepared by the Ministry of Health of Republic of Turkey and the researches on ANC were used in creating the question pool (3-6). Later, in line with the opinions of the experts, HLAT-ANC was developed with 73 items selected from the question pool. Two sections were created, 55 of which were selected from the HLAT-ANC, verbal and 18 were selected, as numerical. The verbal section consists of 4 subdomains, and sub-domains are given below:

Subdomain 1: Healthy lifestyle behaviors during pregnancy(18 questions),

Subdomain 2: Health problems during pregnancy and its consequences (10 questions),

Subdomain 3: Tests to be done during pregnancy (15 questions),

Subdomain 4: Symptoms related to birth and the functioning of the birth process (12 questions).

The verbal section consists of 4 paragraphs with 4 options and sentences in the form of filling the gap, with increasing difficulty. Pregnant women are asked to mark only one of the 4 options, which is the most suitable for each question. Although the three incorrect options in the questions are similar to each other, either they do not comply with grammar rules or their meaning integrity deteriorates when they are brought to a gap in the sentence.

The numerical section consists of a single subdomain and includes 18 questions prepared using hospital forms and medicine box labels. Information cards are presented to the individuals, they are asked to read and ask questions about the cards. Individuals' answers are recorded on the questionnaire form as "correct", "wrong" and "blank".

Correct answers given to the questions in both verbal and numerical sections of HLAT-ANC are evaluated as "1" point, wrong and blank answers are evaluated as "0". No correction formula has been applied regarding "chance-based success".

In our study, the content validity of HLAT-ANC was evaluated with regard to whether it included the sub-topics of HL to be measured in the prenatal period (7). The opinions of 13 experts (three gynecologists and obstetricians, seven public health specialists, two deontologists, and one assessment/evaluation specialist), were consulted in order to validate the HLAT-ANC content. The questions were examined by the experts and each question was evaluated as "necessary-sufficient", "necessary-insufficient" and "unnecessary". In line with the opinions of the experts, although no questions were taken from the HLAT-ANC, revisions were made in the root of the question and its options. Later, expert opinions were transformed into a statistically interpretable form. The content validity ratio (CVR) for each question was calculated by the following formula:

CVR = (Number of experts who say necessary-sufficient / Half of the total number of experts performing the assessment)-1

It is recommended that questions with a CVR calculated as "0" or "negative" calculated in line with expert opinions should be removed from the measurement tool. Since the CVR values calculated in our study were not 0 or negative, no item was removed from the HLAT-ANC. After the CVR was calculated, Content Validity Index (CVI) was calculated for the numerical and verbal parts of the HLAT-ANC. Content Validity Indexes of HLAT-ANC were found to be statistically significant, and content validity was accepted to be sufficient since all of the CVIs calculated for the numerical and verbal parts of HLAT-ANC were greater than 0.67 (8).

A Turkish linguist checked whether the questions constituting the HLAT-ANC were correctly expressed or not and whether there was any wrong in terms of semantics, and after that necessary corrections were made.

A pilot study was conducted on 15 pregnant women who applied to Eskisehir State Hospital Gynecology and Diseases Polyclinics in order to determine whether the questions in HLAT-ANC were understood and possible problems that may be encountered during the application. As a result of the pilot study, it was determined that there was no question that could not be understood in HLAT-ANC. Thereupon, the data collection phase was started in order to carry out the validity-reliability study of the 73-question HLAT-ANC.

The sample size suggested in the development of a new assessment tool is 5-10 times the number of questions in the assessment tool (9). In our study, the sample size was calculated as 511, seven times the number of questions in HLAT-ANC, since the number of questions was 73.

A total of 29 family health centers provide health services in Odunpazari district of Eskisehir province, Turkey. Three of them (Emek, Gokmeydan, and Buyukdere) determined by lot were included in the study. During the study, pregnant women who applied to family health centers for any reason were informed about the subject and purpose of the study. A total of 511 pregnant women who agreed to participate in the study and received verbal consent constituted the study group.

Interviews with pregnant women were conducted in pregnant monitoring rooms of family health centers. It was paid attention that the pregnant follow-up rooms were quiet and calm and that there was no one other than the pregnant woman. The first part of the questionnaire form was filled by the researchers using face to face interview method. The verbal part of the HLAT-ANC in the second part of the questionnaire form was filled by the pregnant women themselves under observation. Later, 11 information cards related to the numerical part of the HLAT-ANC, prepared by the researchers beforehand, were given to the pregnant women respectively, and they were read by the participants. The questions about the information on the cards were directed by the researchers, and the answers given by the pregnant women were recorded in the questionnaire form. There is no time limit for filling out the questionnaire, and this process took approximately 25-45 minutes. A total of 73 pregnant women (32 who did not agree to participate in the study, and 19 illiterate women, and 15 women who were not communicated, and 7 women who healthcare professionals) were not included.

After reaching the calculated 511 pregnant women in order to perform validity and reliability analyzes, the data collection process was terminated.

Validity-Reliability Analysis:

Item Analysis: For item analysis, item difficulty and item discrimination coefficients and comparison methods for item averages for upper and lower 27% were used (7,8,10).

Determination of Building Validity: In the first step, Exploratory Factor Analysis (EFA) was performed to determine the construct validity of HLAT-ANC. Exploratory Factor Analysis,

1) In revealing the factor structure,

2) In determining the items in the factors,

3) It is the totality of methods used to evaluate whether the items are grouped under one or more factors (7).

In order to perform the EFA, it is desirable that the correlation matrix of all variables can be calculated. The tetrachoric correlation matrix was used because of the two-category scoring (true-false / 1-0) of the items in HLAT-ANC (10). Exploratory Factor Analysis was made with a software program called FACTOR, which allows it to work with the tetrachoric correlation matrix.

Bartlett's test of sphericity was used to evaluate the universal significance of the correlation matrix obtained with the EFA (8). In our study, according to Bartlett's test of sphericity, it was seen that HLAT-ANC is suitable for factor analysis.

In our study, the number of the Kaiser-Meyer-Olkin (KMO) was checked to decide whether the sample size was suitable for factor analysis (8). In our study, while doing EFA, all items belonging to the verbal field were not included in the analysis at the same time, and it was tested whether the items in the HLAT-ANC were collected under the factors determined during the development phase. The reason for such an EFA is that the KMO value for 55 items belonging to the verbal domain is lower than 0.60 (9). Since the KMO value of the numerical section is 0.74, all items in this section are included in the EFA at the same time.

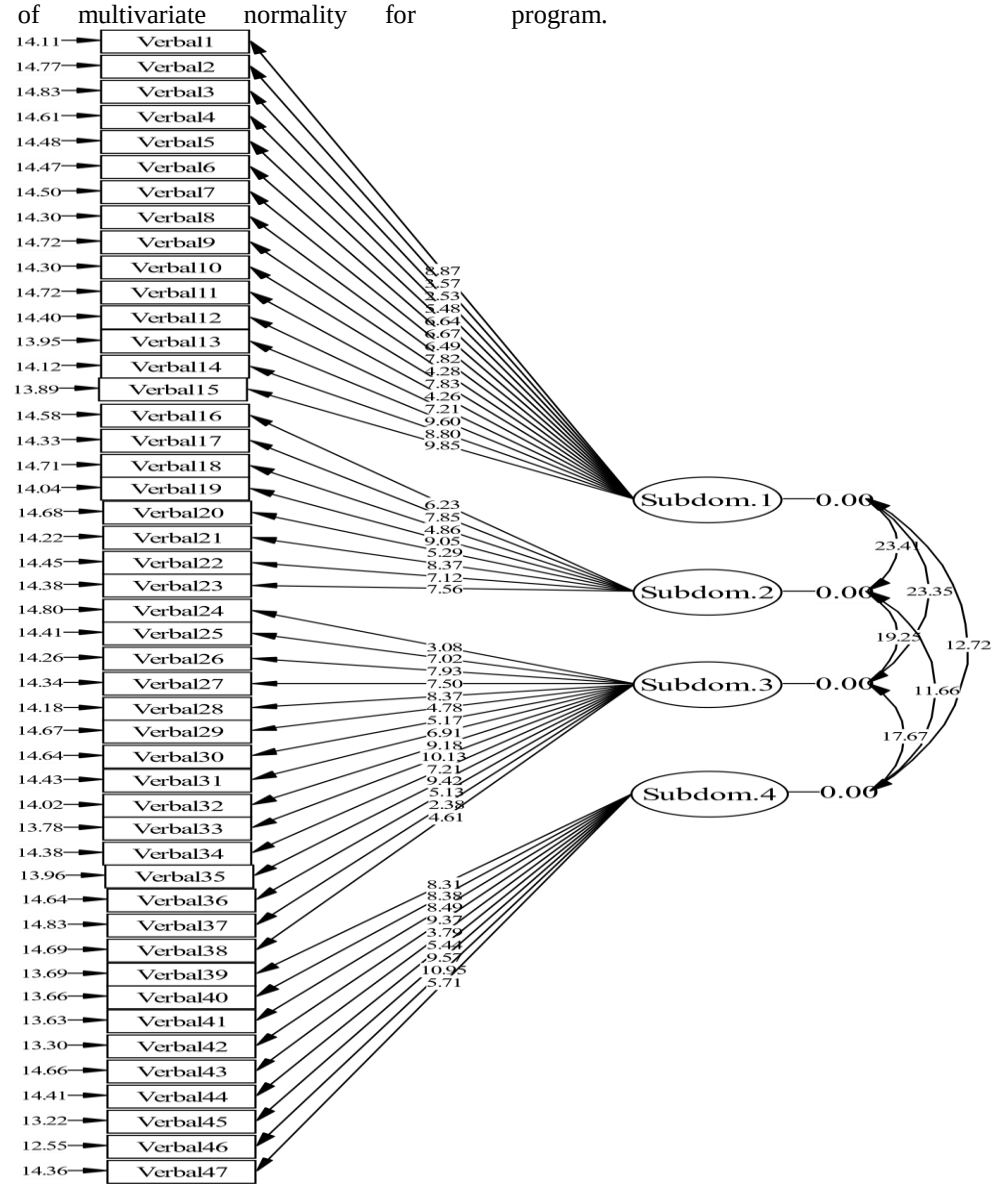
As a result of EFA, 3 items with a factor load below 0.30 were removed from HLAT-ANC (8).

Another method used in determining construct validity is concurrent criterion validity. The correlation coefficient obtained can take values varying between -1 and +1. When the correlation coefficient approaches 1, it gives information about the strength of the relationship and the validity of the developed evaluation tool (8). In our study, "Chew screening questions for health literacy" was taken as the reference test for concurrent criterion validity. Then, the relationship between the scores obtained from both measurement tools was evaluated by Spearman correlation analysis.

In order to test the construct validity of HLAT-ANC with the dissociation method between

groups, it was interviewed with the pregnant women (n = 50) who are health professionals (midwives, nurses, doctors) who are considered to have a high HL level related to prenatal care. Later, the median scores of the pregnant women with and without healthcare professionals in HLAT-ANC were compared with the Mann Whitney U test (8).

Confirmatory Factor Analysis (CFA) is a method that enables the control of factor structures revealed in EFA. While looking at the relationships between the items in the evaluation tool in EFA, the relationships between the factors in CFA are evaluated. CFA is the modeling method used to evaluate the latent structure of a measuring tool, and the fit between observed variables and latent variables is tested (11). In this study, the assumption of multivariate normality for confirmatory factor analysis was tested. Skewness and kurtosis were examined. In addition, a new randomly selected sample (n=444) different from the one in which the exploratory factor analysis was performed. In the implementation of the CFA test, robust maximum likelihood method was applied, taking into account the correlation matrices. As a result of confirmatory factor analysis, the T values of the items are given in Figure 1-2. T value is related to the significance of the load value of each item in the relevant dimension. T- value is > 1.96 for a regression weight, that path is significant at the 0.05 level or better (that is, the estimated path parameter is significant) (11). In this study, the control of the factor structure of HLAT-ANC was done with CFA using LISREL 8.71 software program.



Chi-Square=2177.12, df=1028, P-value=0.00000, RMSEA=0.050

Figure 1. The measurement model for the verbal part of HLAT-ANC (T-values)

Internal Consistency: It is recommended to calculate the Kuder-Richardson-20 (KR-20) coefficient especially in determining the internal consistency of knowledge tests and evaluation tools consisting of two-category evaluations. The fact that the KR-20 coefficient is 0.80 and above

indicates that the internal consistency or reliability of the developed assessment tool is high (7,8). In this study, the determination of the internal consistency of HLAT-ANC was made by calculating the KR-20 coefficient.

Permits: This study consists of the first stage of a thesis study in which HLAT-ANC is developed and the health literacy level of pregnant women is evaluated (Dr. Gulsum OZTURK EMIRAL. "*To Develop an instrument for determination of health literacy levels related to antenatal care, and to determine the health literacy levels for pregnant women*" (Eskisehir Osmangazi University, Medicine School, Public Health Department, Expertise Thesis, Eskisehir, 2018).

The approval of the Non-Invasive Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine, dated February 24, 2016, and numbered 80558721 / G-11.

Statistical Analysis: The data obtained in our study were evaluated in the computer environment in the Statistical Package for Social Sciences version 20.0 (SPSS 20.0). The compliance of the data to normal distribution was evaluated with the Shapiro-Wilk test. Mann Whitney U test, and Spearman correlation analysis were used for statistical analysis of the data in the study. Its validity-reliability was tested by item analysis, exploratory factor analysis (EFA), concurrent criterion validity, intergroup dissociation, and confirmatory factor analysis (CFA), and determination of the Kuder-Richardson-20 (KR-20) coefficient. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The validity and reliability analyzes of HLAT-ANC were conducted on two separate study groups. Item analysis, EFA, KR-20, the separation between groups, concurrent criterion validity, and comparison of item scores for the lower-upper 27% groups were carried out in the study group consisting of 511 pregnant women. CFA was conducted on a separate study group of 444 pregnant women.

It was found that the item discrimination coefficient varied between 0.20-0.57 in the verbal part of HLAT-ANC, and between 0.21-0.48 in the numerical part (for valid items). In the verbal part of HLAT-ANC, items 2, 5, 13, 25, 28, 51, and 54 were removed, while items 1, 12, 16, and 18 were removed from the numerical part (for each one, item discrimination coefficients are less than 0.20). The average difficulty level of HLAT-ANC was calculated as 0.74. According to the item difficulty index, no item was removed from the HLAT-ANC.

Results of Exploratory Factor Analysis: After the item analysis, HLAT-ANC was performed with the remaining 62 items EFA. According to the EFA results, item 47 from the verbal part of HLAT-ANC and items 2 and 4 from the numerical part were removed from HLAT-ANC (because factor loadings were lower than 0.30). In addition, as a result of EFA, it was seen that items 9 and 10 in the numerical section were collected under a separate factor. These items were excluded from HLAT-ANC since a factor should consist of at least three items (109). Although the contribution of items 3, 24, 41, and 42 in the verbal part of HLAT-ANC and item 5 in the numerical part to the common variance was less than 0.20, it was not removed from HLAT-ANC (the reasons for this are factor loads were higher than 0.30, and it has not to narrow the scope of HLAT-ANC). As a result of EFA, items in the verbal section of HLAT-ANC were collected in 4 subdomains, and items in the numerical part were collected in one subdomain.

Internal Consistency: It was found that the KR-20 coefficient for the verbal part of HLAT-ANC ranged from 0.85 to 0.89. For the numerical part, the KR-20 coefficient was calculated as 0.85.

EFA results and KR-20 coefficients of HLAT-ANC are presented in Table 1.

Table 1. EFA results and KR-20 coefficients of HLAT-ANC

Sections of HLAT-ANC	Kaiser-Meyer-Olkin (KMO)	Bartlett's test of sphericity χ^2 ; p	Described variance (%)	Kuder-Richardson-20 (KR-20)
Verbal section				
Subdomain 1	0.80	776.8 ; <0.001	39.36	0.89
Subdomain 2	0.76	298.8 ; <0.001	44.28	0.85
Subdomain 3	0.80	1218.3 ; <0.001	39.00	0.89
Subdomain 4	0.82	652.2 ; <0.001	49.00	0.87
Numerical section	0.74	786.7 ; <0.001	42.00	0.85

Separation between Groups: For the separation method between groups, the median scores of the pregnant women with and without health professionals from HLAT-ANC were compared, and it was determined that the median scores of the health professionals from all subdomains of HLAT-ANC were higher (for each subdomain; $p < 0.05$).

Concurrent Criterion Validity: It was found that there is a weak negative correlation between the scores obtained from all sub-domains of HLAT-ANC and the scores obtained from the Turkish version of Chew screening questions for health literacy (for each one $p<0.05$).

Comparison Methods for Item Averages for Upper and Lower 27%: It was determined that

the scores of the 27% upper group were higher than the 27% lower group in all sub-domains of HLAT-ANC (for each sub-domain; $p < 0.05$).

Results of Comfirmatory Factor Analysis (CFA): After performing the validity and reliability analysis of HLAT-ANC, CFA was performed on a separate data set.

As a result of the CFA performed for the verbal part of the HLAT-ANC, it was found that X2 ÷ SD, Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Error (SRMR) values were within acceptable limits.

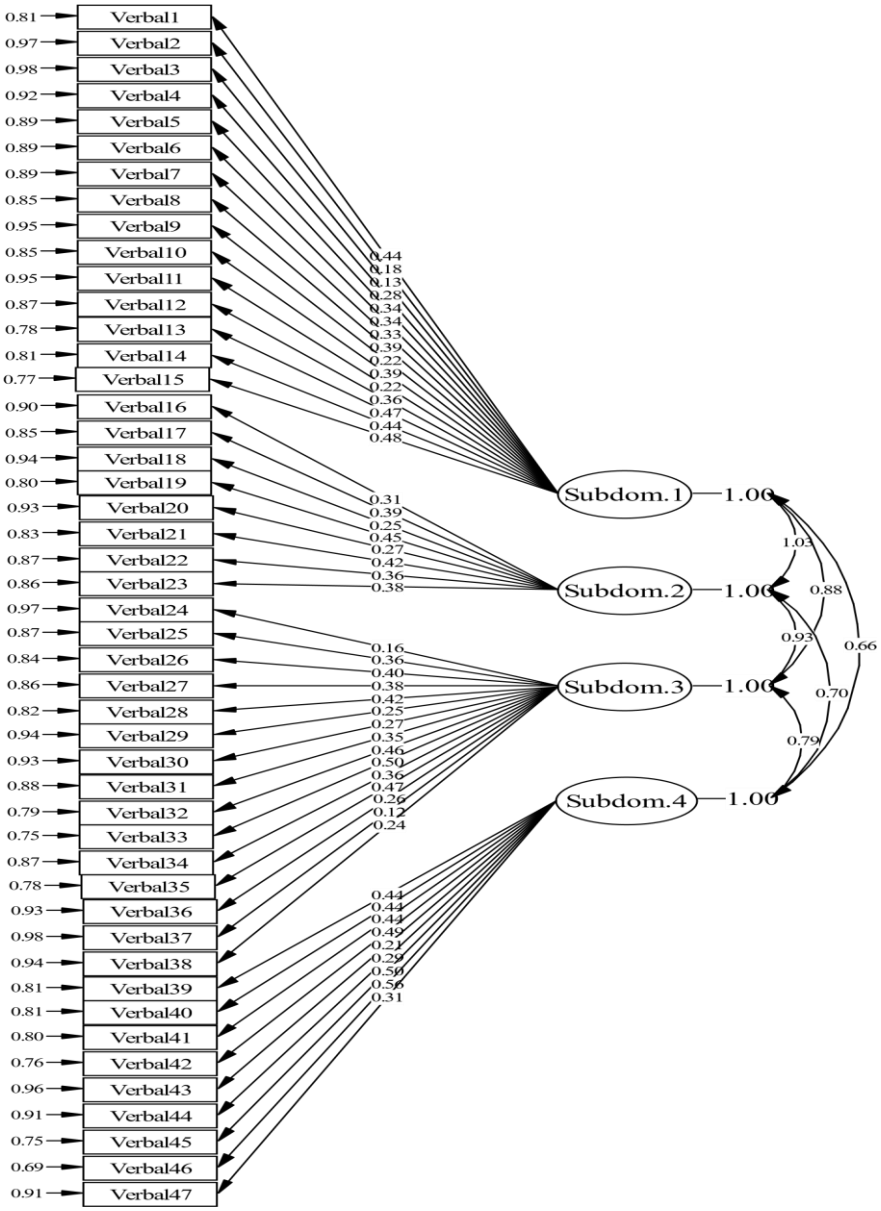
However, it was observed that the Comparative Fit Index (CFI), Goodness of fit Index (GFI), and Adjusted Goodness of fit Index (AGFI) values were not within acceptable limits.

As a result of the CFA, the measurement model for the verbal part of HLAT-ANC and the fit values of this measurement model are presented in Table 2 and Figure 1.

Table 2. Fit indexes obtained for the verbal part of HLAT-ANC as a result of CFA

Fit indexes	**Fit values (Acceptable fit values) of the measurement model obtained for the verbal part of HLAT-ANC**
X^2 ÷ SD	2.12 (≤5)
Root Mean Square Error of Approximation (RMSEA)	0.05 (≤0.08)
Standardized Root Mean Square Error (SRMR)	0.06 (≤0.08)
Comparative Fit Index (CFI)	0.86 (≥0.90)
Goodness of fit Index (GFI)	0.83 (≥0.90)
Adjusted Goodness of fit Index (AGFI)	0.81 (≥0.85)

SD: Standard Deviation



Chi-Square=2177.12, df=1028, P-value=0.00000, RMSEA=0.050

Figure 2. The measurement model for the verbal part of HLAT-ANC (Standardized Solution

As a result of the CFA performed for the verbal part of the HLAT-ANC, it was determined that the standardized factor loads of the items varied between 0.12-0.56 (Figure 2).

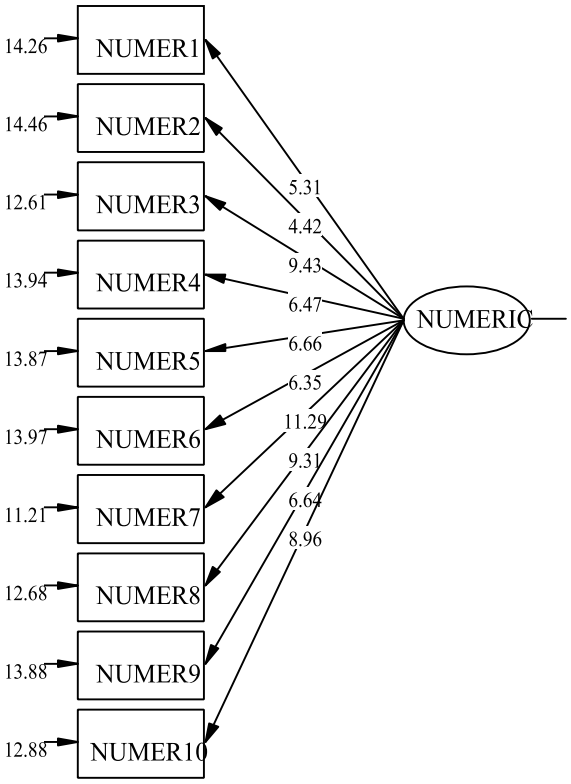
As a result of the CFA performed for the numerical part of the HLAT-ANC, It was determined that the values of all of the fit indices (X2 ÷ SD, RMSEA, SRMR, CFI, GFI and AGFI) were within acceptable limits.

As a result of the CFA, the measurement model for the verbal part of HLAT-ANC and the fit values of this measurement model are presented in Table 3 and Figure 3.

Table 3. Fit indexes obtained for the numerical part of HLAT-ANC as a result of CFA

Fit indexes	Fit values (Acceptable fit values) of the measurement model obtained for the verbal part of HLAT-ANC
X^2 ÷ SD	3.20 (≤5)
Root Mean Square Error Of Approximation (RMSEA)	0.07 (≤0.08)
Standardized Root Mean Square Error (SRMR)	0.05 (≤0.08)
Comparative Fit Index (CFI)	0.90 (≥0.90)
Goodness of fit Index (GFI)	0.95 (≥0.90)
Adjusted Goodness of fit Index (AGFI)	0.92 (≥0.85)

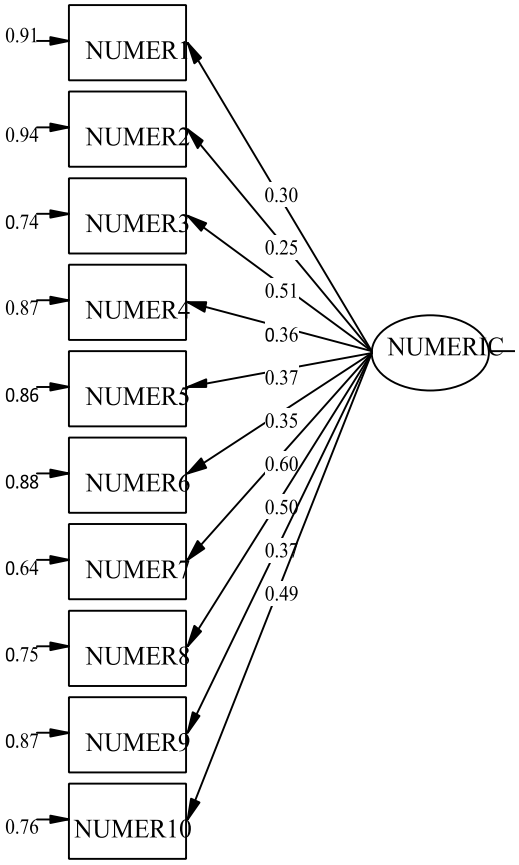
SD: Standard Deviation



Chi-Square=112.05, df=35, P-value=0.00000, RMSEA=0.070

Figure 3. The measurement model for the numerical part of HLAT-ANC (T values)

As a result of the CFA performed for the numerical part of the HLAT-ANC, it was determined that the standardized factor loads of the items varied between 0.25-0.60 (Figure 4).



Chi-Square=112.05, df=35, P-value=0.00000, RMSEA=0.070

Figure 4. The measurement model for the numerical part of HLAT-ANC (Standardized Solution)

Scoring the HLAT-ANC: The scores that can be obtained from the numerical section vary between 0-10. As the scores from each sub-domain of HLAT-ANC increase, the HL level related to each sub-domain also increases.

DISCUSSION

Women are not only responsible for their own health, but also for the health of their families. These responsibilities increase even more during pregnancy. The ability to access, understand, and use accurate health information is extremely important in fulfilling these responsibilities. The ability of pregnant women to access, understand, and use general information about health, and to make appropriate health-related decisions for themselves and their families is closely related to the level of HF (1). It is clear that women with a high level of health literacy will contribute to increasing the health level of themselves, their families, and society.

It is extremely important to determine the extent of the problem by determining the HL levels

for planning health services to increase the HL level of pregnant women. In order to determine the HL level of pregnant women, there should be a standard measurement tool for the prenatal period. As a result of the literature review, no measurement tool was found in print, so it was necessary to develop a new scale. For this reason, in our study, it was aimed to develop HLAT-ANC, to make its reliability and validity.

The purpose of measuring any abstract or concrete feature in research is to evaluate individuals, events, or objects in terms of this feature and to reach certain laws, decisions, concepts, etc. based on the results obtained in the research. One of the important factors affecting the making of correct and appropriate inferences is whether the assessment tools used in research are standard or not. In order for assessment tools to be standard, they must have two basic features, which are described as "validity" and "reliability". Validity; The characteristic that an assessment tool aims to measure is the degree to which it can measure accurately without confusing any other feature. Reliability is; the fact that the test or scale results reveal the conceptual structure correctly is an indicator of the stability of the measurement values obtained in repeated measurements under the same conditions as an evaluation tool (8,12).

In developing a new assessment tool, it is desired that the items to be included in the assessment tools should not be too easy or too difficult. However, if the ease or difficulty of the assessment tool as a whole is important rather than each item to be included in the assessment tool, the average difficulty level should be considered. In order for the assessment tool to be not too easy or too difficult in general, the average difficulty value is desired to be around 0.50 (13). In our study, the average difficulty level of HLAT-ANC was calculated as 0.74. It was reported that the average difficulty level of TOFHLA, which was taken as a basis in the development phase of HLAT-ANC, was 72% in the verbal part, 64% in the numerical part, and 0.68 in the scale (14). In addition, the difficulty level was calculated for each item in the HLAT-ANC in this study. Although the difficulty level of the two items in the numerical part of HLAT-ANC is considered high, they were not removed from the assessment tool because of the high item discrimination coefficients of these items and the average difficulty value of HLAT-ANC at the desired level. A high level of item difficulty may indicate that the item is not always easy, but that the subject is well understood by people. In our study, lower and upper limits were not determined for the difficulty level of the items in the HLAT-ANC, and different analyzes were used in item selection.

The items in the measurement tools that evaluate the characteristics such as ability and success that require individuals to exhibit their maximum performance should be able to distinguish between knowing and unfamiliar people. When developing a new assessment tool, the item discrimination coefficient is required to be at least 0.20 in order for the items to be distinctive and fit for their purpose (10). In this study, insufficiently indistinguishable items were removed from HLAT-ANC. In addition, in our study, item distinctiveness was evaluated by comparing the scores of the sub-top 27% groups, and it was observed that all items in HLAT-ANC were distinctive. As a result, HLAT-ANC consists of relatively easy but highly discriminating substances. One of the reasons why HLAT-ANC is easy maybe that pregnant women are more likely to answer correctly because the substances in HLAT-ANC are specific to the gestational period rather than the general HL level. In the HL index development study conducted by Yang et al. (15), on immigrant married women, it was reported that item discrimination was prioritized in item selection, and even if the items were very easy or difficult, they were not excluded from the index if their discrimination was sufficient. There are also studies reporting similar results in the literature (16,17).

In this study, EFA was used to demonstrate the construct validity of HLAT-ANC. According to Bartlett's sphericity test result obtained with EFA, it was determined that the correlation matrix of the items in HLAT-ANC was suitable for factor analysis, and the sampling adequacy according to the KMO criterion was at a medium-good level. In the scale development studies conducted to determine the HL level in different study groups, it was reported that the suitability of the sample and the correlation matrix to the factor analysis was evaluated by KMO and Bartlett's test of sphericity, similar to our study (18,19).

It was determined that each subdomain of the structure revealed for HLAT-ANC with EFA explained approximately 40% of the variance. Generally, measurement tools are required to explain 50% -70% of the variance, and in social sciences, this value is considered to be "sufficient" to be 40% -60% (8). It was reported that Bjørnsen et al. (20) explained 41% of the variance in the factor structure revealed as a result of EFA in their scale development study conducted to evaluate mental health literacy on adolescents in 2017. Similar results were reported in the study of Hashimoto and Yanagisawa (18). The variance explained by each subdomain of HLAT-ANC was considered sufficient for this study.

Another indicator for the validity of the structure revealed by EFA is the low correlation coefficients between factors (8). The fact that this coefficient is below 0.60 is proof that the factor structure is suitable. The correlation coefficients of the subdomains of the HLAT-ANC verbal part were found to be at the desired level, and the factor

structure of HLAT-ANC was found to be appropriate. In the study conducted by Hashimoto and Yanagisawa on immigrant mothers in Japan in 2011, it was reported that the correlation coefficient between factors was 0.39 in the two-factor scale structure revealed by EFA (18).

The weight of the items in the assessment tool on the factor in which they are included is determined by the factor load. Item factor load ranges from (-1) to (+ 1), and 0.30 is the lowest accepted level (8). In our study, items with a factor load of less than 0.30 were excluded from the assessment tool. It has been revealed that the factor loadings of the items of HLAT-ANC adequately explain the structure to which they belong. In scale development studies on health literacy, it is reported that the minimum values accepted for factor load range between 0.30-0.40 (15,18,20). In our study, all these results obtained with EFA show that the structure validity of HLAT-ANC is ensured.

Another method used in determining the construct validity is that the correlation coefficient between the two assessment tools in concurrent criterion validity is neither too high nor too low (13). In our study, Chew screening questions for health literacy was used for concurrent criterion validity, and it was found that there was generally a weak-moderate negative correlation with subdomains of HLAT-ANC. Similar results from Korea are reported in two different studies conducted by Yang et al. (15,17). In the study conducted by Matsumoto and Nakayama (21), it was reported that the correlation level between the HL scales used was good. In the validity and reliability study of Yin et al. (22), Chew screening questions for health literacy were used for concurrent criterion validity, and it was reported that a weak negative correlation was found between the two scales in the USA. It is expected that the correlation coefficients between the scores obtained from Chew screening questions for health literacy and the scores from HLAT-ANC will be negative. High scores from Chew screening questions for health literacy mean that the perceived HL level is low; High scores from HLAT-ANC indicate a high HL level. One of the reasons for the weak-medium correlation between the two measurement tools may be that the items of Chew screening questions for health literacy are Likert-type, statement-based, and reflect the individual's typical responses. Additionally, it may be that it measures the HL perceived by the individual. However, since HLAT-ANC is a measurement tool that individuals should show their maximum performance, individuals may not be able to give correct answers to items when addressing multiple-choice items. Therefore, it is normal that the correlation coefficient between the two-scale scores is low.

The separation between groups is one of the methods used in determining the construct validity in validity and reliability studies. In our study for this method, we compared the HLAT-ANC scores of pregnant women with and without healthcare professionals, with the thought that their HL levels would be high due to the high health-related education levels of health professionals. It was observed that those who were health professionals had a higher level of HL related to the antenatal period. This result supports that the structure validity of HLAT-ANC is ensured. Similar results have been reported in the scale development studies for evaluating HL in the literature (17,20). The higher the internal consistency coefficients in validity and reliability studies, the higher the consistency of the items in the assessment tool with each other. In general, an internal consistency coefficient of at least 0.70 is recommended for an assessment tool to be considered reliable (8). In our study, it was found that the reliability levels of all subfields of HLAT-ANC were high. In Turkey, Ozdemir et al (23) in a study, it was reported that the internal consistency coefficient of 0.70. In the study of Bilgel et al. (24), it was reported that the internal consistency coefficients varied between 0.77-0.89 in the subdomains of the scale.

In the study in which Yin et al. (22), evaluated the parenteral HL level, a scale scored similarly to the HLAT-ANC developed in our study was used and the internal consistency coefficient was reported to be 0.64. There are studies reporting different results in the literature (25,26). The reasons such as the difference of the scoring systems of the scales used in the studies and the size of the study groups in which the studies were conducted may be the reasons why different internal consistency coefficients are reported in the literature.

CFA, which is a modeling method, is performed in order to verify the scale structure determined by fictionalized or other analyzes. In Confirmatory Factor Analysis (CFA), more than one statistical criterion is used to evaluate the fit between observed variables and latent variables. However, there is no consensus on which criteria should be used and what the predictive values of these criteria should be (27). In our study, for the verbal part of HLAT-ANC, the harmony values of RMSA, SRMR, and X2 ÷ SD are high; CFI, GFI, and AGFI fit values were found to be at acceptable levels. It was observed that all fit values obtained for the numerical part of HLAT-ANC were at high levels (11,28,29). In some studies, RMSA, SRMR, and X2 ÷ SD values were frequently examined as criteria of compliance and it was reported that the obtained results were similar to our study (21,26). However, since GFI and AGFI values may vary according to the characteristics of the study groups, they are mostly not recommended to be used as a fit criterion (27,30). Since the fit criteria obtained in our study are among the acceptable or even good fit limits, it can be said that the measurement model

established with CFA has a high degree of compliance with the data.

CONCLUSION

As a result, it has been concluded that HLAT-ANC meets the standards required to be accepted as a scale and is a valid and reliable measurement tool. Raising the HL level has become one of the primary issues of public health in the protection and improvement of maternal and child health and in improving health outcomes. The first step of the studies to increase the HL level is to determine the current HL level of women. The HLAT-ANC developed in this study can be used to determine the HL levels of different study groups.

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RESEARCH ARTICLE

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Comparison of Hematological and Biochemical Parameters and Cardiovascular Risk Scores in Patients Applying to the Obesity Outpatient Clinic

ABSTRACT

Objective: The aim of this study was to compare hematological and biochemical parameters and cardiovascular risk scoring in patients admitted to the obesity outpatient clinic.

Methods: In this descriptive cross-sectional study, data of the patients who admitted to the Obesity Outpatient Clinic of Duzce University Research and Application Hospital between 2017 and 2018 were evaluated retrospectively. Age, gender, smoking status, presence of Diabetes Mellitus (DM), and body mass index (BMI) were recorded and the cardiovascular risk of the patients was calculated by using the scoring system of the European Society of Cardiology (ESC) and Turkish Society of Cardiology (TSC).

Results: A total of 631 participants were included in the study. The mean age was 38.9±12.1 (min=21, max=65) and 75.1% of the patients were female and 24.9% were male. It was observed that 19.2% of the patients were smokers, 4.6% had DM and 36.9% had insulin resistance. When the patients were evaluated according to the BMI scores, it was found that 3.3% of them were underweight, 7.3% were normal weight, 22.5% were overweight and 66.9% were obese. According to TSC risk scoring system, 51.4% of the patients were in low risk, 20.5% were in medium risk and 28.1% were in high risk category. According to the ESC risk scoring system, 83.5% of the patients were in low risk, 10.9% were in medium risk and 5.5% were in high risk category. According to both risk scoring systems, there were significant differences between the risk groups in terms of age, gender, BMI, and presence of DM ($p<0.001$). When evaluated according to the TSC risk score, it was seen that the patients in the high-risk category had a lower platelet/lymphocyte ratio and a higher total cholesterol/HDL ratio. According to both risk scoring systems, no correlation was found between cardiovascular risk and RDW, MPV, leukocyte count, and NLR(Neutrophil-Lymphocyte ratio).

Conclusions: Conducting a cardiovascular risk assessment for patients who admit to primary health care services for obesity counseling is important. A cardiovascular risk assessment conducted at admission may help some precautions to be taken earlier. There is a need for more studies to determine easily accessible parameters that can predict cardiovascular risk.

Keywords: Obesity, BMI, NLR, PLR, Cardiovascular Risk Scores, Hematological Parameters.

Obezite Polikliniğine Başvuran Hastalarda Hematoljik ve Biyokimyasal Parametrelerle Kardiyovasküler Risk Skorlarının Karşılaştırılması

ÖZET

Amaç: Bu çalışmada, obezite polikliniğine başvuran hastalarda; hematolojik ve biyokimyasal parametreler ile kardiyovasküler risk skorlamasının karşılaştırmalı değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Tanımlayıcı-kesitsel olarak planlanan bu araştırmada, Düzce Üniversitesi Araştırma ve Uygulama Hastanesinin Obezite Polikliniğine 2017-2018 yılları arasında başvuran hastaların, dosya verileri retrospektif olarak değerlendirildi. Hastaların yaş, cinsiyet, sigara kullanımları, DM tanılarının varlığı, BKİ değerleri kaydedildi; kardiyovasküler risk faktörleri Avrupa ve Türkiye Kardiyoloji Dernekleri risk skorlamasına göre değerlendirildi.

Bulgular: Çalışmaya %75,1'i kadın, %24,9'u erkek, 631 katılımcı dahil edilmiştir. Yaş ortalaması 38,9±12,1 (min=21-maks=65) olarak bulunmuştur. Hastaların %19,2'sinin sigara kullandığı, %4,6'sında DM ve %36,9'unda insülin direnci olduğu görülmüştür. Katılımcıların %3,3'ü zayıf, %7,3'ü normal kilolu, %22,5'i fazla kilolu ve %66,9'u obezdir. Türkiye Kardiyoloji Derneği risk skorlamasına göre hastaların %51,4'i düşük , %20,5'i orta ve %28,1'i yüksek risklidir. Avrupa Kardiyoloji Derneği risk skorlamasına göre ise hastaların %83,5'i düşük, %10,9'u orta ve %5,5'i yüksek risklidir. Her iki risk skorlamasına göre risk grupları arasında yaş, cinsiyet, beden kitle indeksi ve DM varlığı açısından anlamlı farklılık görüldü ($p<0,001$). Türkiye Kardiyoloji Derneği risk skorlamasına göre; yüksek risk grubunda olanların daha düşük trombosit/lenfosit oranına ve daha yüksek total kolesterol/HDL oranına sahip olduğu görüldü. Her iki skorda da kardiyovasküler risk ile RDW, MPV, lökosit sayısı, nötrofil/lenfosit oranı değerlerinde ilişki saptanmadı.

Sonuç: Birinci basamak sağlık hizmetlerine obezite danışmanlığı için başvuran hastalara risk değerlendirmesi yapılması önemlidir. Yapılan kardiyovasküler risk değerlendirmesi ile bazı önlemlerin erkenden alınması sağlanabilir. Riskin erken saptanması amacıyla klinisyenlerin kolay ulaşabilecekleri parametreleri ortaya çıkaracak daha çok çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Obezite, BKI, NLR, PLR, Kardiyovasküler Risk Skorları, Hematolojik Parametreler.

INTRODUCTION

The main task of family physicians is first of all primary prevention and to help the diagnosis, treatment, follow-up and palliative care process of the diseases (1). Obesity is one of the most common diseases in the society with an increasing prevalence, can be prevented with primary prevention, which is one of the main tasks of family medicine. According to the 2016 data of the World Health Organization, the prevalence of obesity has tripled in the last 40 years. The prevalence of obesity constitutes 13% of the adult population (2). The potential diseases that obesity can cause include cardiovascular diseases, diabetes, and chronic systemic diseases. Obesity and dyslipidemia are frequently seen concomitantly. As the patient's weight problem increases, the probability of developing dyslipidemia also increases. This coexistence increases the importance of dyslipidemia screening in obese patients. The main parameters which have been used in screening are Triglyceride, LDL (low-density lipoprotein), HDL (high-density lipoprotein), and total cholesterol (3). Obesity causes cardiovascular diseases, especially heart failure, coronary artery disease, and atrial fibrillation,by causing inflammation and atherosclerosis (4).

It is important to make prospective cardiovascular risk estimations by determining the risks in terms of cardiovascular events in the population. Risk factors for cardiovascular diseases can be divided into two groups including alterable risk factors and inalterable risk factors. Inalterable risk factors include age, gender, and family history and in alterable risk factors include physical inactivity, sedentary life, obesity, smoking, diabetes mellitus, hypertension, and dyslipidemia (5). Various risk models and calculators have been developed over the years to estimate the cardiovascular risks. Cardiology societies also approve the use of models with the highest practical utility and accuracy in clinical practice. The reasons why certain risk calculators are more commonly used include ease of use, applicability to the clinician's patient population, measured outcomes, and professional community recommendations. By using current technological facilities, online calculation systems that can calculate the risk by entering the characteristics and examinations of the patients have been created. The online Cardiovascular Risk Calculation system created by the Turkish Society of Cardiology (TSC) and the online HeartScore system created by the European Society of Cardiology (ESC) for Turkey are practical evaluation systems used in the clinical practice. However, it has been stated that there are problems in terms of scoring systems and classical markers used in CVD risk assessment currently (6). The facts that these scoring systems, which are prominent in the literature, yield different risk scores for each population, the risk ratios that change with age, and they require continuous updating, suggest that new markers should be investigated to estimate cardiovascular risk (7,8).

Cardiovascular diseases have high mortality rates and also cause high cost health expenses, therefore clinicians working in primary health care institutions need tests that can signal the initial stage of the disease, enable the disease to be diagnosed earlier, and help to take measures earlier. Hemogram and biochemistry tests are the simplest and easiest to reach tests that clinicians can use in primary care. In this study, we aimed to examine whether the hematological and biochemical parameters that are available in primary health care institutions can be helpful in the earlier diagnosis of cardiovascular risk in patients who admit to the obesity outpatient clinics.

MATERIAL AND METHODS

This study is designed as a descriptive, cross-sectional, and retrospective study. The patients who admitted to the obesity outpatient clinic, between January 01st, 2017 and March 31st, 2018 and between the ages of 18 and 65 were included in the study. Demographic characteristics of the patients, existing characteristics that are thought to be associated with cardiovascular disease risk, BMI and blood test parameters were evaluated, retrospectively.

Cardiovascular Risk Calculation System: It was prepared by the Turkish Society of Cardiology, based on data from the Framingham Heart Study of the U.S. National Heart Lung and Blood Institute's to help calculate the risk of cardiovascular events within 10 years. The Cardiovascular Risk Calculation System consist of 7 questions, which includes age, LDL, HDL, systolic and diastolic blood pressures, the presence of comorbid diabetes, and whether the patient smokes or not, respectively. After determining the gender of the patient, the score and percentage of patients are determined as low, intermediate or high risk specific to the mean age range (9).

HeartScore System: The 'SCORE' system has been developed as a result of the joint decisions of the European Society of Cardiology, the European Society of Hypertension, the European Atherosclerosis Society and other societies, according to the data of 12 cohort studies conducted in Europe with different cardiovascular risk levels, since 1994. The HeartScore system we have been using is an easy-to-use, interactive form of SCORE risk charts developed and suitable for online calculation. In order to predict fatal cardiovascular events over a 10-year period, it evaluates risk factors including age, gender, systolic blood pressure, total cholesterol and HDL cholesterol values, and smoking status. According to this scoring system the risk is classified as low, intermediate, high, and very high. Regardless of

other risk parameters, if the systolic blood pressure is above 180 or the total cholesterol level is above 309 the patient is accepted to be in the high risk group (10).

Statistical Analysis: Normal distribution prerequisite was examined with Kolmogorov-Smirnov and Shapiro-Wilk tests, and kurtosis and skewness coefficients were checked. Levene test was used for variance homogeneity. In the comparisons of the groups One-Way ANOVA and post hoc LSD tests were used. Pearson chi-sqaure test was used in the analysis of categorical data and multiple comparisons were examined with Bonferroni correction. Descriptive statistics are given as mean and standard deviation for numerical data, and as numbers and percentages for categorical data. Statistical analyzes were performed by using SPSS v.22 package program. A value of p> 0.05 was accepted statistically significant.

RESULTS

A total of 631 patients were included in the study; 474 (75.1%) of them were female and 157 (24.9%) were male. The mean age of the patients was 38.9±12.1 (min=21-max=65). It was found that 121 (19.2%) patients were smokers. DM was present in 29 (4.6%) and insulin resistance was present in 233 (36.9%) patients. While there was no DM in 369 (58.2%) patients. When the BMI scores of thew patients were evaluated, it was found that, 21 (3.3%) patients were underweight, 46 (7.3%) were normal weight, 142 (22.5%) were overweight, and 422 (66.9%) patients were obese (Table 1).

Table 1. Comparison of the demographic characteristics, smoking status, the presence of DM, and BMI of the participants

		Number	%
Age, Mean ±SD		38.9±12.1	
Gender	Female	474	75.1
	Male	157	24.9
Smoking status	Yes	121	19.2
	No	510	80.8
DM	No DM	369	58.5
	DM	29	4.6
	Insulin resistance	233	36.9
BMI	Underweight	21	3.3
	Normal	46	7.3
	Overweighed	142	22.5
	Obese	422	66.9

DM: Diabetes Mellitus, BMI: Body Mass Index SD: Standard Deviation

According to the risk scoring of the Turkish Society of Cardiology, 231 (51.4%) patients were at low risk, 92 (20.5%) were at intermediate risk, and 126 (28.1%) were at high risk. On the other hand, according to the risk scoring of the European Society of Cardiology, 527 (83.5%) patients were at low risk, 69 (10.9%) were at intermediate risk, and 35 (5.5%) were at high risk (Table 2).

Table 2. Distribution of cardiological risk scores of the patients

		Number	%
TSC risk score	Low	231	51.4
	Intermediate	92	20.5
	High	126	28.1
ESC risk score	Low	527	83.5
	Intermediate	69	10.9
	High	35	5.5

When the risk groups according to the TSC score were evaluated, it was found that the mean age of the patients in the intermediate risk group was the highest and the mean age of those in the low risk group was the lowest. There were significant differences between the groups in terms of age, and these differences were due to the differences between all risk groups (p<0.001). When the risk groups were compared in terms of BMI scores it was found that there were significant differences between the groups, and this differences were due to the differences between the low-risk group and the other two groups (p<0.001). It was found that the mean BMI of the patients in the low risk group was the lowest. In addition, 13.9% of the patients in the low risk group, 54.3% of those in the intermediate risk group, and 31.7% of those in the high risk group were are males. There was a significant difference between the groups in terms of gender (p<0.001). When the groups were compared in terms of the presence of DM, it was found that 0.4% of the patients in the low risk

group, 4.3% of those in the intermediate risk group, and 16.7% of those in the high risk group had DM, and the presence of DM increased significantly as the risk increased (p<0.001). When the groups were compared in terms of smoking status, it was found that 13% of the patients in the low risk group, 17.4% of those in the intermediate risk group and 34.1% of those in the high risk group were smokers. There was a significant difference between the groups in terms of smoking status, and it was determined that the rate of smokers was the highest in the high risk group (p<0.001, Table 3).

Table 3. Comparison of the cardiological risk scores of the patients according to various characteristics (TSC Score)

	Low (n=231)	Intermediate (n=92)	High (n=126)	P
Age	40.36±8.92[a]	51.77±8.61[b]	46.50±9.79[c]	**<0.001**
BMI	32.85±5.97[a]	35.67±6.56[b]	36.18±5.85[b]	**<0.001**
Gender				
Male	32 (13.9)[a]	50 (54.3)[b]	40 (31.7)[c]	**<0.001**
Fermale	199 (86.1)[a]	42 (45.7)[b]	86 (68.3)[c]	
DM				
None	149 (64.5)[a]	51 (55.4)[ab]	58 (46.0)[b]	
Present	1 (0.4)[a]	4 (4.3)[b]	21 (16.7)[c]	**<0.001**
Insulin resistance	81 (35.1)[a]	37 (40.2)[a]	47 (37.3)[a]	
Smoking status				
Non smoking	201 (87.0)[a]	76 (82.6)[a]	83 (65.9)[b]	**<0.001**
smoking	30 (13.0)[a]	16 (17.4)[a]	43 (34.1)[b]	

DM: Diabetes Mellitus, BMI: Body Mass Index

When the risk groups according to the TSC score were evaluated in terms of laboratory results, it was found that there were significant differences between the risk groups in terms of platelet/lymphocyte ratios (p=0.001). The mean platelet/lymphocyte ratio of the patients in the low-risk group was higher than the other two groups. It was determined that this difference was due to the difference between the low-risk group and the other two groups. In addition, there were significant differences between the risk groups in terms of T.cholesterol/HDL ratio (p<0.001). It was determined that this difference was due to the difference between the low-risk group and the other two groups; the T. cholesterol/HDL ratio was significantly lower in the low-risk group compared to the other two groups (Table 4).

Table 4. Comparison of the laboratory result according to the cardiological risk groups (TSC Score)

	Low (n=231)	Intermediate (n=92)	High (n=126)	p
RDW	13.83±1.12	13.80±0.97	13.73±1.09	0.714
MPV	8.40±0.97	8.44±0.83	8.41±0.95	0.939
Leucocyte	7.38±1.51	7.43±1.86	7.77±1.51	0.074
NLR	1.96±1.01	1.83±0.76	1.86±0.9	0.403
PLR	124.75±55.65[a]	106.62±29.01[b]	111.21±32.99[b]	**0.001**
T.cholesterol/HDL	3.79±0.92[a]	4.75±0.93[b]	5.03±1.15[b]	**<0.001**

RDW: Red blood cell distribution width, MPV: Mean platelet volume, NLR: Neutrophile / lymphocyte ratio, PLR: Platelet/ lymphocyte ratio

When the risk groups according to the ESC score were evaluated, it was found that the mean age of the patients in the high risk group was the highest and the mean age of those in the low risk group was the lowest. The differences between the groups in terms of age were significant, and these differences were due to the differences between all risk groups (p<0.001). it was found that the mean BMI of the patients in the low risk group was the lowest, and the mean BMI of those in the high risk group was the highest. The differences between the risk groups were significant and these differences were due to the differences between all risk groups (p<0.001). In addition, the differences between the groups in terms of gender were significant (p<0.001). It was found that 20.5% of the patients in the low risk group, 44.9% of those in the intermediate risk group, and 51.4% of those in the high risk group were male. When the groups were compared in terms of the presence of DM, it was found that 3.4% of the patients in low risk group, 7.2% of those in the intermediate risk group, and 17.1% of those in the high risk group had DM, and the presence of DM increased significantly as the risk increased (p<0.001). When the groups were compared in terms of smoking status, it was found that 18.8% of the patients in the low risk group, 18.8% of those in the intermediate risk group and 25.7% of those in the high risk group were smokers. There was no significant difference between the groups in terms of smoking status (p=0.600, Table 5).

Table 5. Comparison of the demographic characteristics, smoking status, the presence of DM, and BMI of the participants (ESC score)

	Low (n=527)	Intermediate (n=69)	High (n=35)	p
Age	35.39±9.54[a]	54.74±6.46[b]	62.06±4.50[c]	**<0.001**
BMI	32.23±6.95[a]	36.20±6.53[b]	37.11±7.08[c]	**<0.001**
Gender				
Male	108 (20.5)[a]	31 (44.9)[b]	18 (51.4)[b]	**<0.001**
Female	419 (79.5)[a]	38 (55.1)[b]	17 (48.6)[b]	
DM				
None	319 (60.5)[a]	33 (47.8)[a]	17 (48.6)[a]	
Present	18 (3.4)[a]	5 (7.2)[ab]	6 (17.1)[b]	**0.001**
Insulin resistance	190 (36.1)[a]	31 (44.9)[a]	12 (34.3)[a]	
Smoking status				
Non smoker	428 (81.2)	56 (81.2)	26 (74.3)	0.60
smoker	99 (18.8)	13 (18.8)	9 (25.7)	0

DM: Diabetes Mellitus, BMI: Body Mass Index

When the risk groups according to the TSC score were evaluated in terms of laboratory results, it was found that there were significant differences between the risk groups in terms of platelet/lymphocyte counts (p=0.004). It was determined that this difference was due to the difference between the low-risk group and the intermediate-risk group. The mean platelet/lymphocyte ratio of the patients in the low-risk group was higher than the intermediate-risk group. In addition, there were significant differences between the risk groups in terms of T.cholesterol/HDL ratio (p<0.001). It was determined that this difference was due to by the difference between the low-risk group and the other two groups; the T. cholesterol/HDL ratio was significantly lower in the low-risk group compared to the other two groups (Table 6).

Table 6. Comparison of the laboratory result according to the cardiological risk groups (ESC Score)

	Low (n=527)	Intermediate (n=69)	High (n=35)	p
RDW	13.83±1.17	13.80±0.84	13.83±0.94	0.984
MPV	8.38±0.92	8.61±1.05	8.33±0.91	0.145
Leucocyte	7.60±1.70	7.17±1.61	7.57±1.90	0.141
NLR	1.94±0.84	1.80±0.65	1.92±0.92	0.447
PLR	122.05±45.11[a]	106.25±31.55[b]	107.51±29.64[ab]	**0.004**
T.cholesterol/HDL	3.99±1.11[a]	4.86±0.97[b]	4.88±0.99[b]	**<0.001**

RDW: Red blood cell distribution width, MPV: Mean platelet volume, NLR: Neutrophile / lymphocyte ratio, PLR: Platelet/ lymphocyte ratio

DISCUSSION

In this study, the demographic characteristics, BMI values, smoking status, presence of DM, laboratory findings at the time of admission and cardiovascular risk scores of the patients who admitted to obesity outpatient clinic were compared. The most important finding of our study is that approximately half of the patients who admitted to the obesity outpatient clinic had intermediate and high cardiological risk. We found that, 28.1% of the patients were at high-risk according to the risk score of the Turkish Society of Cardiology, and 20.5% of them at intermediate risk. In addition, according to the risk score of the European Society of Cardiology, 5.5% were considered at high risk and 10.9% were at intermediate risk. Considering that the vast majority of our patients were overweight and obese, these high ratios of risk were expected. Such a difference in risk scoring may be related to the fact that both risk scores measure with different sensitivity for different age groups. Age is among the cardiovascular risk factors and is considered to be a non-modifiable risk factor. Advancing age has been associated with an increased risk of disability in activities of daily living and cardiovascular diseases (11). The risk of a cardiovascular disease increases with age (12). In a cohort study 3.6 million individuals aged 40 and over were screened in terms of CVD and it was reported that the prevalence of all vascular diseases increases significantly in each decade of life (13). In a large-scale cohort study conducted in Finland, by Jousilahti et al. (14), it was found that the risk of CVD increases with age. In a study conducted by Uçar (15), the CVD risk scores of patients who admitted to the Family Medicine Outpatient Clinic were examined and it was observed that the risk scores increased as the age increased. Similarly, in our study, the mean age of the patients in the high risk group was found to be higher. The increase in age is thought to be due to the increase in the formation of atherosclerotic plaque, over time.

According to the results of our study, the platelet/lymphocyte ratio was significantly lower in

the high risk group compared the other two groups and T. cholesterol/HDL ratio was significantly higher in the high-risk group compared to the other two groups, when evaluated according to the TSC score. On the other hand, when the groups were evaluated according to the ESC score it was found that the platelet/lymphocyte ratio was higher in the low-risk group compared to the medium-risk group. Platelet/lymphocyte ratio (PLR) is a new prognostic marker that brings together the independent effects of these 2 parameters. It provides insight into both aggregation and inflammation pathways and may be more valuable in estimating coronary atherosclerotic burden than platelet or lymphocyte counts alone. PLR has been identified as a potential marker of the balance between thrombosis and inflammation and has been associated with increased cardiovascular morbidity and mortality.

Increased circulating platelet and decreased lymphocyte numbers have been associated with increased cardiovascular morbidity and mortality (16). It has been shown that a low number of blood lymphocyte is associated with worse cardiovascular outcomes in patients with CAD and chronic heart failure (17, 18). In addition, it has been shown that there is a relationship between circulating platelet count and major adverse cardiovascular outcomes in healthy adults as well as patients with CAD (19, 20). Our results, which are consistent with the literature, will provide help to predict the cardiovascular risks of the patients by using the hemogram tests which can be performed easily and in a short time in primary care services. The fact that our study results are also compatible with the cardiovascular risk scores used by clinicians supports the effective use of the hemogram test.

In our study, the T. Cholesterol /HDL ratio was found to be significantly higher in the high-risk group. The importance of the measurement and interpretation of LDL and HDL levels are emphasized in US National Cholesterol Education Program guidelines, since there is strong evidence that a high concentration of LDL in plasma is atherogenic and a high level of HDL is cardioprotective (21, 22).

However, measuring all these parameters individually and separately and evaluating the risk accordingly includes the bias of not being able to control the parameter that is not measured. For this reason, the ratio between these parameters has been calculated in order to evaluate various risks. Total cholesterol/HDL ratio and LDL/HDL ratio have been used for this purpose (23). Kinosian et al. (24) reported that the total cholesterol/HDL ratio was a superior tool for the evaluation of risk for CAD compared to total cholesterol or LDL cholesterol levels separately, and the authors suggested that current practice guidelines could be more efficient, if the risk stratification was based primarily on this ratio rather than LDL cholesterol level. Similarly, Onat et al. (25), in their prospective evaluation, concluded that the TC/HDL ratio is the only significant independent lipid variable in predicting future coronary death events. Söğüt et al. (26) compared the patients with angiographically detected CHD and those without CHD in terms of various variables and found that TC/HDL ratio was significantly higher in patients with angiographically detected CHD. The result of our study is compatible with the literature and the TC/HDL ratio gives very valuable information in terms of CVD risk.

Limitations: Although our study included a relatively high number of patients, it reflects only a local area results. In this context, it should be noted that we cannot generalize our results. Prospective studies with larger samples are needed to clearly define the relationship between PLR and CVD risk.

CONCLUSION

Our study results show that hemogram and biochemical tests, which can be performed easily and provide short-term results in primary care, can be used to predict cardiovascular risk. Studies generally make a limited examination of the disease when assessing CVD risk. However, studies in which all CVD risks are evaluated together will provide insight for the determination of the dimensions of the relationship.

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RESEARCH ARTICLE

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Short-Term Effect of Kinesio Taping on Neck Pain and Disability in Patients with Loss of Cervical Lordosis: A Randomized Controlled Study

ABSTRACT

Objective: The patients with loss of cervical lordosis have weakened neck extensors. This study aimed to investigate the effect of Kinesio taping, applied to the cervical extensors, on neck pain and disability in patients with loss of cervical lordosis.

Methods: A total of 111 patients with neck pain due to loss of cervical lordosis completed the study (54 Kinesio tape group, 57 control group). All patients were given paracetamol 1500 mg/day for four days. Additionally, the Kinesio tape group received one session of Kinesio taping treatment. Neck pain intensity was assessed using the Visual Analogue Scale, and neck disability was evaluated using the Neck Disability Index. The measurement points were baseline and day 4.

Results: Visual Analogue Scale and Neck Disability Index scores were similar at baseline. Statistically significant improvements in the levels of pain and disability were observed in both groups; however, there was further change in the Kinesio tape group ($p<0.001$).

Conclusions: Kinesio taping is effective in achieving improvement of significant pain and neck disability symptoms related to loss of cervical lordosis.

Keywords: Kinesio Taping, Cervical Lordosis, Pain, Disability.

Servikal Lordoz Kaybı Olan Hastalarda Kinesio Bantlamanın Boyun Ağrısı ve Sakatlık Üzerindeki Kısa Dönemli Etkisi: Randomize Kontrollü Bir Çalışma

ÖZET

Amaç: Servikal lordoz kaybı olan hastaların boyun ekstansör kaslarında zayıflama olmaktadır. Bu çalışmanın amacı, servikal lordoz kaybı olan hastalarda servikal ekstansör kaslarına uygulanan Kinesio bantlamanın hastaların boyun ağrısı ve sakatlık üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Servikal lordozda kaybı olan toplam 111 hasta çalışmayı tamamladı (54 hasta Kinesio bant grubu, 57 hasta kontrol grubu). Tüm hastalara dört gün boyunca 1500 mg/gün parasetamol tablet verildi. Ek olarak, Kinesio bant grubuna bir seans Kinesio bantlama tedavisi uygulandı. Hastaların boyun ağrısı şiddeti Görsel Analog Skala, boyun sakatlığı şiddeti ise Boyun Özür İndeksi kullanılarak değerlendirildi. Hastaların değerlendirmeleri tedavinin başlangıç günü ve 4. gün yapıldı.

Bulgular: Tedavi öncesi hastaların Görsel Analog Skala ve Boyun Özür İndeksi skorları benzerdi. Tedavi sonrası her iki grupta boyun ağrısı ve sakatlık düzeyi skorlarında istatistiksel olarak anlamlı iyileşmeler gözlendi. Bununla birlikte Kinesio bant grubundaki iyileşmenin daha anlamlı olduğu gözlendi ($p<0.001$).

Sonuç: Kinezyo bantlama, servikal lordoz kaybıyla ilişkili boyun ağrısı ve boyun sakatlığı iyileştirilmesinde etkili bir tedavidir.

Anahtar Kelimeler: Kinezyo Bantlama, Servikal Lordoz, Ağrı, Sakatlık.

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INTRODUCTION

Loss of cervical lordosis or straight cervical spine is a common finding visible on lateral cervical x-ray, and this condition is a cause of structural overload and degeneration of muscles, tendons, and discs in the cervical region (1). It is not entirely understood why cervical lordosis decreases, but atrophic (2) or weakened (3) neck extensors and laminoplasty (4) are proposed contributors. Besides clinical symptoms like neck pain (5) and dizziness (6), loss of cervical lordosis is associated with reduced vertebral artery hemodynamics (7). On the other hand, some individuals with loss of cervical lordosis are asymptomatic, too (8). Various treatment methods, including spinal manipulation (9), cervical extension traction (6), and neck extensor exercises (10), have been explicitly used to restore cervical lordosis and improve clinical symptoms in patients with loss of cervical lordosis. However, there is currently no standardized treatment approach for the condition.

Kinesio taping is a therapeutic and rehabilitative clinical method applied to patients. It was developed by a Japanese chiropractor, Dr. Kenzo Kase, in the 1970s to help relieve pain and restore injured soft tissues. Today, this method has become increasingly popular, and many clinicians use it to improve a variety of musculoskeletal and other disorders such as injury, pain, dysfunction, and lymphedema (11-13). It has been suggested that Kinesio taping has multiple mechanisms of action, including changes in muscular activity and tension supporting muscles, reduction of nociceptive stimuli causing pain relief, proprioceptive facilitation and segmental stabilization, and activation of lymphatic drainage (11-15).

To the best of our knowledge, no previous study has investigated the role of Kinesio taping specifically in patients with loss of cervical lordosis. However, patients with loss of cervical lordosis have atrophic (2) and weakened neck extensors (3), and the mechanism of action of Kinesio taping also includes muscle support (11-13). Accordingly, Kinesio taping applied to support the neck extensors may be useful in patients with loss of cervical lordosis. Therefore, this study aimed to investigate the effect of Kinesio taping on neck pain and disability, specifically in patients with loss of cervical lordosis.

MATERIAL AND METHODS

This study was designed as a short-term, prospective, non-blinded, randomized controlled trial with two measurement points (baseline and day 4). By the principles of the Declaration of Helsinki, the study was carried out at the University Faculty of Medicine Department of Physical Medicine and Rehabilitation between April 2017 and August 2017. Approval from the Ethics committee and institutional permissions were obtained for the implementation of the research (Decision No: 2017-5/13; Institution permission date: April 12, 2017), and written informed consent was obtained from each participant.

All patients with loss of cervical lordosis with acute neck pain (pain duration ≤3 months) were evaluated by the same physiatrist for eligibility. Loss of cervical lordosis was determined on the standard lateral cervical x-ray by using the posterior tangent technique measuring the total cervical curvature, which refers to the angle between lines drawn parallel to the posterior surface of the C2 and C7 vertebrae. We considered the ″loss of cervical lordosis″ for this angle as +4º to –4º (16).

Patients aged <18 or >40 years or who have the following medical conditions were excluded: chronic neck pain (pain duration >3 months), normal cervical lordosis (lordosis angle<-4º), cervical kyphosis (lordosis angle>+4º), cervical vertebral anomalies, inflammatory rheumatic diseases, neck injury or surgery, cervical herniated disc or radiculopathy, obesity, and psychiatric illness. The patients were randomly assigned into two groups using sequentially numbered cards by helpful staff. The evaluation tools were a 10-cm visual analog scale (VAS) and the Turkish version of the Neck Disability Index (NDI), which are used for the evaluation of neck pain and disability (17). The NDI, a scale made up of 10 items, is a self-assessment inventory designed to evaluate self-perceived pain and disability. The higher the score, the greater the perceived pain and disability. The ten items include neck pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and leisure activities (17).

All patients were given paracetamol 1500 mg/day for four days. Additionally, the Kinesio tape group received one session of Kinesio taping treatment for four days, while the control group received no additional therapy. Two Y-shaped tapes, one on each side of the cervical spine and the trapezius muscles, were applied horizontally. The remaining Y-shaped tape was attached vertically to the cervical spine (Figure 1).

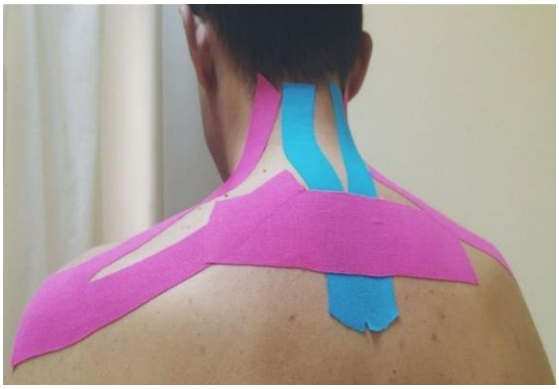

Figure 1. Application of Kinesio taping

Statistical Analysis: IBM SPSS Statistics 16 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. The Kolmogorov-Smirnov normality test was used to determine whether the continuous data were normally distributed. In the intergroup comparisons of continuous variables, the Student's t-test was used for normally distributed variables, while the Mann-Whitney U test was used for variables with non-normal distribution. The paired t or Wilcoxon tests were performed for the intragroup comparisons of continuous variables considering the normality test results. Categorical variables were evaluated by the Chi-square test and were presented as numbers (percentage). Continuous data were presented as mean (SD) (min.-max.). $p<0.05$ was considered statistically significant.

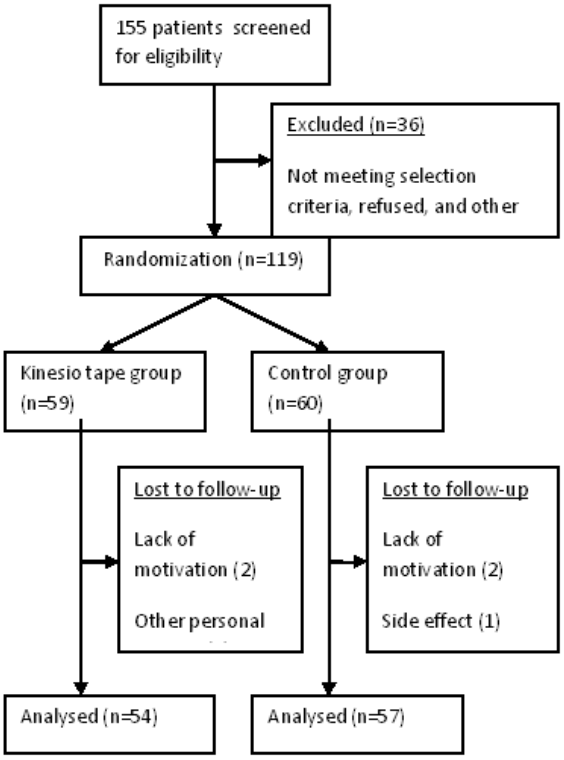

Figure 2. The Flow of Study Participants

RESULTS

Figure 2 presents the flow diagram demonstrating the study progression. A total of 155 neck pain patients with loss of cervical lordosis were screened for eligibility. Out of the 119 patients who met the selection criteria and were randomized to the treatment groups, 111 completed the study (54 Kinesio tape group, 57 control group) (Figure 2).

In both groups, most patients were female, approximately 65-67%. In addition, the two groups were similar in terms of patient baseline characteristics, including age, sex, body mass index, cervical lordosis angle, and neck pain and disability scores ($p>0.05$) (Tables 1 and 2).

Table 1. The Characteristics of Participants

	Kinesio tape (n=54)	Control group (n=57)	p
Age, years	26.87 (7.37)	25.91 (5.81)	0.447
Gender, F/M	35/19	38/19	0.837
BMI, kg/m^2	25.94 (2.06)	26.53 (1.93)	0.127
Angle (°)	0.13 (2.76)	0.35 (2.88)	0.682

BMI: Body mass index, **Angle (°):** Cervical lordosis angle according to the posterior tangent technique, Values are given as mean (SD) or number.

In both groups, in all evaluation parameters (neck pain severity during rest and motion and neck disability scores), significant improvements were found on the fourth day compared with baseline ($p<0.001$). When considering the difference between the two groups in the amount of change from baseline to day 4, the Kinesio tape group was more effective than the control group for improving pain and disability ($p<0.001$) (Table 2).

Table 2. Neck Pain Severity and Neck Disability

	Kinesio Tape Group (n=54)	Control Group (n=57)	p1
VAS (rest)			
Baseline	7.37 (0.90) (4-9.5)	7.16 (0.99) (4.5-8.2)	0.625
Fourth day	2.32 (1.59) (0-8.5)	4.93 (1.28) (0-8)	
Difference	5.05 (1.68)	2.22 (1.42)	<0.001
p2	<0.001	<0.001	
VAS (motion)			
Baseline	7.70 (0.84) (4-9.6)	7.51 (0.91) (4.5-8.9)	0.329
Fourth day	2.49 (1.72) (0-9)	5.25 (1.47) (0-10)	
Difference	5.21 (1.65)	2.25 (1.53)	<0.001
p2	<0.001	<0.001	
NDI			
Baseline	15.76 (6.15) (3-24)	15.18 (5.93)	0.612
Fourth day	7.09 (3.66) (0-20)	10.89 (6.28)	
Difference	8.67 (5.98)	4.28 (5.80)	<0.001
p2	<0.001	<0.001	

NDI: Neck Disability Index, VAS: Visual analog scale, p1: Intergroup comparison; p2: Intragroup comparison in each group between baseline and fourth day. Values are given as mean (SD) when using the parametric test and given as mean (SD) (min.-max.) when using the non-parametric test.

DISCUSSION

In our study, our results suggest that combined Kinesio taping and paracetamol have a more substantial positive effect on neck pain and disability than paracetamol alone in managing the loss of cervical lordosis. Previous studies of the Kinesio taping effect in patients with neck pain

have revealed conflicting results (18-22). Ozkan et al. also suggested that Kinesio taping significantly improves the VAS, NDI scores, cervical range of motion, and cervical lordosis angles. They claimed that the combination of therapeutic exercise and Kinesiotaping is beneficial in reducing pain and disability and improving range of motion and cervical lordosis loss in patients with chronic non-specific neck pain (18). González-Iglesias et al. reported that Kinesio taping improved neck pain and cervical range of motion in patients with acute whiplash injury (19). Similarly, Ay et al. shown that Kinesio taping improved neck pain and mobility in patients with cervical myofascial pain syndrome (20). On the other hand, Saavedra-Hernández et al. reported that cervical thrust manipulation and Kinesio taping have similar effects on neck pain and disability in patients with mechanical neck pain (21). Similarly, Puerma-Castillo et al. obtained no evidence of additional benefits from using Kinesio taping in addition to conventional treatment in patients with neck pain (22). However, the present study and the studies mentioned above differ somewhat in their specific topics. In addition, thanks to its focus on the loss of cervical lordosis, the present study is different and original.

Although its mechanism of action is not yet clear, Kinesio taping may have a combination of inhibition and activation functions, including reduced nociceptive stimuli and pain inhibition, decreased muscle fatigue and soreness, increased muscle activation, proprioceptive facilitation, enhanced healing of injured tissues, correction of fascial dysfunction and po¬sition, increased segmental stability, activation of blood flow and lymphatic drainage (11-15). Given that one of the effects of Kinesio taping is muscle support (11-13) and loss of cervical lordosis is associated with weakness of the neck extensors (2,3), there are reasonable grounds for using the Kinesio taping applied to support the neck extensors in patients with loss of cervical lordosis. In addition, it has been found that cervical stabilization is provided predominantly by the neck musculature (80%) (23), and proprioceptive and contractive balance of muscles contributes to maintaining spinal stability (24,25). For these reasons, and considering the loss of cervical lordosis is related to cervical muscle imbalance, including extensor muscle weakness (2,3), the positive effect of Kinesio taping on neck pain and disability in patients with the condition may be via proprioceptive facilitation and muscle activation leading to increased cervical muscle balance. Since altered cervical spine alignment is a cause of abnormal vertebral kinematics potentially leading to altered sensorimotor integration through an altered afferent input from the cervical spine soft tissues (6), the corrective effect of Kinesio taping on this abnormal information from sensory afferents in the straight cervical spine may have played an important role in improved neck pain and disability.

On the other hand, the present study has some potential limitations. Because we did not include sham taping in the study, the placebo effect of the application cannot be ruled out. Besides this, due to some selection criteria used in the study design, such as age (>18-<40 years), lordosis angle (+4º to –4º), and pain duration (acute, ≤3 months), the study results cannot be generalized to all patients with loss of cervical lordosis. Nevertheless, the used selection criteria provide sufficient clarity and certainty on the interpretation of study homogeneity.

CONCLUSION

In conclusion, Kinesio taping as an addition to paracetamol provides significant additional benefits on neck pain and disability in patients with loss of cervical lordosis. Considering that the Kinesio taping can be recommended as a complementary treatment option for more successful management of loss of cervical lordosis.

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RESEARCH ARTICLE

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Evaluation of Clinical, Radiological and Functional Outcomes of Surgically Treated Ankle Fractures

ABSTRACT

Objective: The ankle is an important joint in the walking function of the body. Surgical treatment is required in cases where displaced and unstable fractures and joint compatibility cannot be achieved by conservative methods. The main goal of surgical treatment is to restore the anatomical position of the talus within the ankle for a normal tibiotalar joint relationship.

Methods: 73 patients who were admitted to our outpatient clinics between January 2006 and October 2015, who were diagnosed with ankle fracture and underwent surgical treatment, were retrospectively evaluated and compared with the intact ankle.

Results: Of the patients who had surgery; Bimalleol fracture in 34 (46.58%), trimalleol fracture in 8 (10.96%), lateral malleolar fracture in 14 (19.18%), medial malleolar fracture in 13 (17.81%), with posterior malleolar fracture in 1 ankle dislocation (1.37%) and 1 had posterior malleolar fracture with medial malleolus fracture (1.37%). According to the Lauge Hansen classification, the most common type of SER (Supination External Rotation) fracture (14 cases) (19.18%), followed by the second most common PER (Pronation External Rotation) fracture type (14 cases) (19.18%). According to the Danis - Weber classification, Type C (21 cases) (52.50%) was the most common and Type B (14 cases) (35.00%) was the second most common. When the union time was analyzed according to the fracture type, no statistically significant difference was observed (p=0.064).

Conclusions: If surgical treatment is applied in ankle fractures the length of the fibula should be ensured, rigid internal fixation should be made with the aim of anatomical reduction of the joint surface, and ankle movements should be started early.

Keywords: Adult, Ankle Fracture, Surgical Treatment.

Cerrahi Tedavi Uygulanmış Ayak Bileği Kırıklarının Klinik, Radyolojik ve Fonksiyonel Sonuçlarının Değerlendirilmesi

ÖZET

Amaç: Ayak bileği vücudun yürüme fonksiyonunda önemli bir eklemdir. Deplase ve stabil olmayan kırıkların ve eklem uyumunun konservatif yöntemlerle sağlanamadığı durumlarda cerrahi tedavi gerekir. Cerrahi tedavinin temel amacı, normal bir tibiotalar eklem ilişki için talusun ayak bileği içindeki anatomik pozisyonunu sağlamaktır.

Gereç ve Yöntem: Ocak 2006-Ekim 2015 tarihleri arasında polikliniğimize başvuran, ayak bileği kırığı tanısı alan ve cerrahi tedavi uygulanan 73 hasta retrospektif olarak sağlam ayak bileği ile karşılaştırıldı.

Bulgular: Ameliyat olan hastalardan; 34'ünde bimalleol kırığı (%46.58), 8'inde (%10.96) trimalleol kırığı, 14'ünde lateral malleol kırığı (%19.18), 13'ünde medial malleol kırığı (%17.81), 1'inde posterior malleol kırığı ile birlikte ayak bileği çıkığı (%1.37) ve 1'inde de medial malleol kırığı ile birlikte arka malleol kırığı vardı (%1.37). Lauge Hansen sınıflamasına göre en sık SER (Supinasyon Eksternal Rotasyon) kırık tipi (14 olgu) (%19.18), ardından ikinci en sık PER (Pronasyon Eksternal Rotasyon) kırık tipi (14 olgu) (%19.18) görüldü. Danis - Weber sınıflamasına göre en sık Tip C (21 vaka) (% 52.50) ve ikinci en sık Tip B (14 vaka) (% 35,00) görüldü. Kaynama süresi kırık tipine göre incelendiğinde istatistiksel olarak anlamlı farklılık gözlenmedi (p=0,064).

Sonuç: Ayak bileği kırıklarında cerrahi tedavi uygulanacaksa fibula uzunluğu sağlanmalı, eklem yüzeyinin anatomik olarak redükte edilmesi amacıyla rijit iç tespit yapılmalı ve ayak bileği hareketlerine erken başlanmalıdır.

Anahtar Kelimeler: Yetişkin, Ayak Bileği Kırığı, Cerrahi Tedavi.

INTRODUCTION

It is aimed to achieve anatomical reduction in ankle fractures even with surgical methods to protect the reduction until the fracture heals, and to restore normal function in the pre-injury period with a painless movable ankle (1-4). The main purpose of surgical treatment is to provide the anatomical position of the talus within the ankle for a normal tibiotalar relationship. The most important factors affecting the results of the treatment in ankle fractures are the fracture type, the number of fractured malleolus, the adequacy of the reduction and the age of the patient (5,6). Studies have shown that the fibula plays a key role in the reduction of ankle fractures and the lower tibiofibular ligaments are extremely important in ankle physiology. Failure to fully reduce the lateral malleolus and talar tilt are the main factors that lead to bad results (7). One of the factors causing complications in ankle fractures is diastasis of syndesmosis and enlargement of the mortis. Considering the fracture of the lateral malleolus and the type and level of the lower tibiofibular syndesmosis lesion, different surgical methods and implants are recommended (8). The purpose of this study was to evaluate the results of surgical treatment of ankle fractures and to compare the clinical, radiological and functional outcomes.

MATERIAL AND METHODS

Seventy-three patients who were hospitalized with the diagnosis of ankle fracture and underwent surgical treatment were included. Preoperative evaluation of the patients was made by standard AP (Anteroposterior) radiographs (Figure 1), lateral ankle radiographs (Figure 2), mortis radiographs and Computed Tomography (CT). The fracture types (isolated medial/lateral/posterior malleol or their combination) were evaluated by these methods. The patients were evaluated retrospectively in terms of functional and radiological aspects.

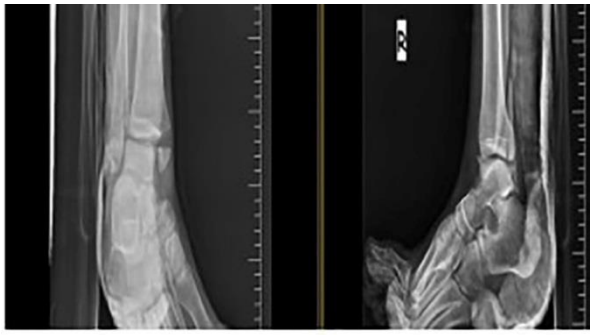


Figure 1. Preop Ap-Lateral ankle radiography

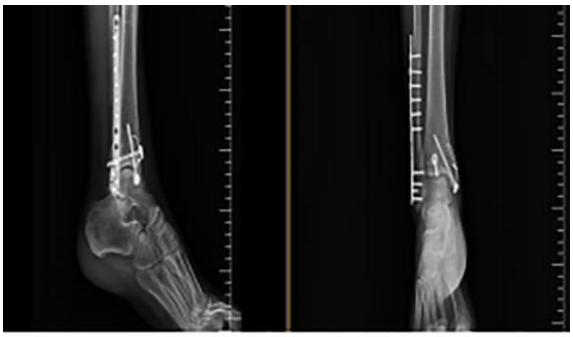


Figure 2. Postop Ap-Lateral ankle radiography

All of the patients included in the study were 18 years of age or older, and all had only one-sided ankle fracture. Ap-Lateral ankle radiographs were used for the postoperative evaluation of the patients (Figure 3).

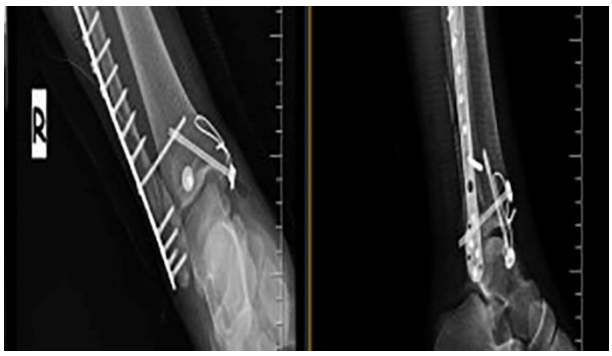
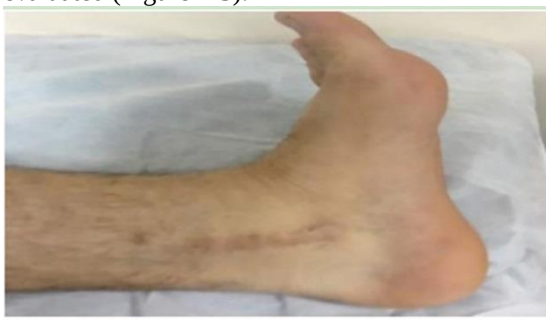
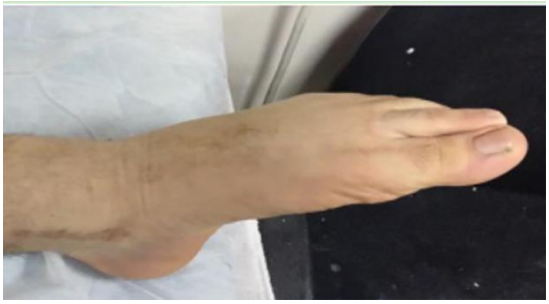


Figure 3. Malleol screw or cortical screw was used as fixation material radiography

Other accompanying extremity fractures, fracture etiology, fracture complications, range of motion after fracture union on physical examination, time to union, technique applied, fracture type, duration of treatment, hospitalization and start time, and functional results of the fractured side according to the healthy ankle were evaluated (Figure 4-5).



Figüre 4. Ankle dorsiflexion



Figüre 5. Ankle plantar flexion

In the surgical treatment, it was aimed to have the talus in anatomical position under the tibial joint surface. Even slight displacement of the talus was not accepted as it would lead to degenerative changes. Our treatment approach was surgical treatment in displaced bimalleolar fractures, displaced lateral malleolus fractures more than 2 mm and 1-2 mm enlargement in the mortis.

In cases with bimalleolar and trimalleolar fractures, the lateral malleolus was first fixed. . In cases with lateral malleolus fracture, the internal malleolus fracture was fixed after fixation of the lateral malleolus fracture. If the posterior malleolus fragment was more than 25% of the joint surface or was displaced more than 2 mm, it was surgically fixed. In patients who underwent surgical treatment for the posterior malleolus fracture, after the lateral malleolus fracture was fixed, the posterior malleolus was reached by advancing subperiostally towards the back. Following the reduction of the posterior malleolus, a small incision was made from the front (fixed with 1 screw from front to back). Fixation was applied to all cases with syndesmosis injury. Malleol screw or cortical screw was used as fixation material. The screw was sent either over the plate applied to the outer malleolus or directly over the fibula, parallel to the plafond, from posterolateral to anteromedial. Care was taken for the transfixation screw to hold the medial cortex of the tibia and pass it 2-3 cm above the plateau. The syndesmosis screw was tightened with the ankle in full dorsiflexion.

Short leg splint was applied to the patients after the operation. Sutures of the patients were removed on the postoperative 15th day. Parenteral antibiotics were given to the patients until discharge after surgery and oral antibiotherapy was started after discharge. The dressing was applied every other day until the sutures were removed. Active ankle exercises were started in the 4-6th week in cases with union, and partial weight was given after the removal of splints. Full load was allowed after complete union was seen on radiographs taken at the 10-12th week.

Functional Assessment: Orthopedic examinations of all patients who came for control were done and AP, lateral and mortis radiographs of the ankles were taken. The evaluation of the cases was done separately according to the Weber, AOFAS and Freiburg protocols.

RESULTS

The preoperative waiting period was found to be shorter in patients with a high Weber and AOFAS scores. Although it is not statistically significant according to all 3 scoring systems, the rate of bad results increases with the prolongation of the preoperative waiting period.

When we look at the distribution of postoperative late complications by fracture types, 20 of 34 patients with bimalleolar fractures had late complications. We encountered late complications after surgery in 2 patients with lateral malleolar fractures, 1 patient with medial malleolar fracture, 2 patients with posterior + medial malleolar fractures, and 1 patient with posterior malleolar fractures + ankle dislocations, and 1 patient with trimalleolar fractures (Table 1).

Table 1. Distribution of late postoperative complications by fracture type

	Late complication		Arthritis		Sudeck Atrophy		Tibiofibular Synostosis		Fibular Shortness		Wound Problem		Syndesmosis Screw Breakage		Total	
BF	17	73.91%	8	80%	6	75%	4	100%	1	50%	2	0%	1	50%	34	46.58%
LMF	2	8.70%	0	0%	0	0%	0	0%	0	0%	2	12.5%	1	50%	14	19.18%
MMF	1	4.35%	0	0%	0	0%	0	0%	1	12.5%	0	0%	0	0%	13	17.81%
TF	1	4.35%	1	10%	0	0%	0	0%	0	0%	0	0%	0	0%	8	10.96%
P+MF	1	4.35%	1	10%	1	12.5%	0	0%	0	0%	0	0%	0	0%	3	4.11%
PMF + AD	1	4.35%	0	0%	1	12.5%	0	0%	0	0%	0	0%	0	0%	1	1.37%
Total	23	100%	10	100%	8	100%	4	100%	2	25%	4	12.5%	2	100%	73	100%

BF: Bimalleolar fracture; LMF: Lateral malleolar fracture; MF: Medial malleolar fracture; TF: Trimaleolar fracture; P+MF:Posterior+ malleolar fracture; PMF + AD: Posterior malleolar fracture + ankle dislocation

When the patients with postoperative late complications were examined according to Weber classification, 2 patients with Weber A type, 2 patients with Weber B type and 7 patients with Weber C type were found. According to the Lauge-Hansen classification, 2 patients with SAD type, 2 patients with SER type, 5 patients with PER type, and 2 patients with PAP type were determined. When evaluated according to the Weber scoring protocol, 42 patients had poor results, 22 patients had good results, and 9 patients had excellent results. Excellent improvement was found to be statistically significantly higher in the 18-42 age group ($p = 0.029$) (Table 2).

Table 2. Distribution of Weber protocol results by age groups

WEBER	18-42 age		43-60 age		>60 age <		Total		
Great	5	14.29%	1	2.86%	3	8.57%	9	25.71%	**0.029**
Good	11	31.43%	9	25.71%	2	5.71%	22	62.86%	0.937
Bad	19	54.29%	20	57.14%	3	8.57%	42	120.00%	0.288
Total	35	47.95%	30	41.10%	8	10.96%	73	100.00%	

Patients scoring AOFAS a Rated by me protocol; Poor results were obtained in 5 patients and good results were obtained in 68 patients.

When the patients were evaluated according to the Freiburg scoring protocol, good results were obtained in 57 patients, moderate results in 14 patients and poor results in 2 patients (Table 3).

Table 3. Distribution of the FREIBURG protocol by age groups

FREİBURG	18-42 Yaş		43-60 Yaş		>60 Yaş		Toplam		p
Good	27	77.14%	23	76.67%	7	87.50%	57	78.08%	0.791
Medium	8	22.86%	5	16.67%	1	12.50%	14	19.18%	0.720
Bad	0	0.00%	2	6.67%	0	0.00%	2	2.74%	0.229
Total	35	47.95%	30	41.10%	8	10.96%	73	100.00%	

The mean union time for the fractures was found to be 10.22±2,31(6-14) weeks.there was not any statistically significant relationship between union time and fracture type (p<0.064).

When the patients are evaluated according to Weber protocol; Excellent results were obtained in 9 patients, good results in 21 patients, and poor results in 43 patients. Poor result was found significantly higher in bimalleolar fracture according to Weber. According to the Weber scoring protocol, excellent results were found to be significantly higher in lateral malleolus fractures (Table 4).

Table 4. Distribution of results by fracture type (Weber)

	Weber						
Fracture Type	**Great**		**Good**		**Bad**		**p**
Bimalleolar fracture	2	22.22%	5	23.81%	26	60.47%	**0.007**
Trimaleolar fracture	2	22.22%	2	9.52%	5	11.63%	0.611
Medial malleolar fracture	0	0.00%	7	33.33%	5	11.63%	0.844
Lateral malleolar fracture	4	44.44%	6	28.57%	5	11.63%	**0.048**
Medial+posterior malleolar fracture	1	11.11%	1	4.76%	1	2.33%	0.475
Posterior malleolar fracture + ankle dislocation	0	0.00%	0	0.00%	1	2.33%	0.702

Good results were found to be high in the simple fall group according to the Weber protocol (40.9%). Poor outcome was higher in the simple fall group according to the AOFAS protocol. Good results were higher in the simple fall group according to the Freiburg protocol (39.6%).

The mean AOFAS score of patients who had bimalleolar fractures and transfixed with a syndesmosis screw was 84.45, and the mean AOFAS score of those who could not be transfixed with a syndesmosis screw was 80.41. The AOFAS score of patients who had lateral malleolus fractures and transfixation with a syndesmosis screw was 92.33, and the AOFAS score of patients who were not transfixed with a syndesmosis screw was 91. The AOFAS score of patients with a trimalleolar fracture, whose posterior malleolus was fixated, was 92.11.

DISCUSSION

Ankle injuries can range from a simple soft tissue trauma or ligament injury to a complex fracture-dislocation or even traumatic amputation. In many studies, it has been emphasized that anatomical reduction is important for a good result after ankle fractures, and the type of fracture and treatment method will affect this reduction (9).

In order to get a good result in the treatment of ankle fractures, the fracture must be stabilized anatomically in the early period and early joint movement must be initiated. Some authors argue that if anatomical reduction is achieved with conservative methods, surgical treatment will not be required (10,11). In our clinic, surgical treatment is applied in cases where full anatomical reduction cannot be achieved with conservative methods in ankle fractures with intra-articular extension.

Our average time until the operation is 5.38 days. Although this period is a little longer; it is compatible with the 4.2-8.4-day periods given in the literature (12-14). Carrage et al. recommended early surgical treatment in high-energy ankle fractures, because more soft tissue problems were

seen in cases delayed for more than 24 hours (15). Fogel et al. showed that in patients with ankle fracture, the reduction would be wrong in most of the cases where surgical treatment is delayed for more than 1 week (16). Breederveld et al and Koontrath et al. evaluated the effect of delaying surgical treatment and found that there was no significant difference in results in the delayed group (1,17,18). In our study, it was observed that the average waiting period of patients with poor results in FREIBURG, AOFAS and WEBER ankle scoring systems was longer.

In cases where the medial clear space is more than 4 mm, syndesmosis or damage to the deltoid ligament is considered. Again, if the tibiofibular overlap is less than 10 mm in anteroposterior radiographs, this is an indication that syndesmosis is impaired (19,20). After the lateral malleol fixation is completed in surgery, stress test should be performed under fluoroscopy control with lateral rotation and forced eversion, and those with syndesmosis instability should be treated. In our study the syndesmosis damage was fixed by one 3.5 mm screw from the plate in 37 cases, 2 screws from the plate in 1 case, 1 free screw in 3 cases and 2 free screws in 1 case.

Early mobilization and early weight-bearing affect the results positively by preventing the adhesions (21). The recommended time for weight-bearing in cases with transfixation screws is seen to vary between 6-8-12 weeks in the literature (11-22). The patients in our study, weight bearing started in an average of 8 weeks and there was no loss of reduction. Synovial adhesion, arthritis and sudeck atrophy were observed in 10 cases where movement and weight bearing started late.

Mandracchia et al. think that maintaining fibula length and alignment has a major role in stabilizing the talar component of the ankle (11). Lateral plating is a common surgical treatment method for lateral malleolar fractures; however, complications such as wound infection and necrosis of the wound lips have been reported with a rate of 11% related to this technique (23). In elderly and osteoporotic patients, lateral plate increases wound healing problems and causes poor fixation (24). There are publications reporting that the quality of fixation can be increased in osteoporotic fractures with supportive methods and combined application of locked lateral plates (25). It has been shown that posterior plating is not mechanically different from lateral plating in osteoporotic elderly patients. Minihane et al. found that the posterior plates provided better biomechanical stability over the lateral plating (26). Işık et al. showed that surgical techniques with lateral plates and tension bands used in Danis-Weber Type A and B fractures yield excellent results and the tension band technique can be an inexpensive and acceptable treatment option in such fractures (27). For the patients in our study lateral plate-screw osteosynthesis was performed (except for 1 patient) and union was detected in all of them. Posterior plating was not preferred due to the risk of peroneal tendon irritation.

One of the common complications after ankle fracture surgery is skin problems around the incision (28). Wound and skin problems occurred in 4 patients in our study after surgery. Recovery was achieved with local debridement and dressings. Another complication that can be seen is reflex sympathetic dystrophy (29). Prolonged inactivity after surgery sets the stage for this. In our study; Reflex sympathetic dystrophy occurred in 8 (10.96%) patients.

It has been reported that the prognosis is poor in PER type injuries of the ankle (3-30). Roberts applied surgical treatment to 25 patients with malleolar fractures and reported the average follow-up results of 1.5 years, found poor results in PER type injuries in his study (31). He stated that the reason for this was that syndesmosis was not fully healed by complete ligamentous tear in PER type injuries. Yılmaz et al. stated that 31 cases at the end of an average of 26 months of follow-up had poor results in PER type injuries and the best results were in SER type injuries (32). In our study, while poor results were higher in PER injury according to Weber, good results were found to be more according to Aofas and Freiburg classifications.

Isolated posterior malleolus fractures constitute 1% of all ankle fractures and are associated with axial compression or plantar flexion injury that ankle fracture classification systems do not include (33-35). In ankle fractures accompanying posterior malleolar fractures, less satisfactory functional results are seen in relation to the size of the fractured fragment (36,37). Fixation of the posterior malleolus has been recommended in cases with trimalleolar fractures in which the posterior malleolus contains more than 25% joint surface and the talus is subluxated posteriorly more than 2 mm, and it has been reported that the size of this undetected fragment may cause poor functional results (14,30,38-40). In 9 cases with trimalleolar fractures in our study, since the posterior fragment contains more than 25% of the joint surface, it was fixed with 1 malleolar screw and the functional results of these patients were good.

CONCLUSION

As a result; we found that the rate of good results was high in patients with ankle fracture after a simple fall in etiology. We think that in patients with bimalleolar and trimalleolar ankle fractures, the fibular fixation should be done firstly and this may affect the ankle results more positively. Functional scores and results of trimalleolar fractures were found to be good. The reason for this is; it was thought that the good outcome rate in the ankle was significantly higher with posterior malleolar fracture stabilization. We also found that

the ankle functions were better in patients who started early motion. Patients who underwent surgical treatment as soon as possible had better functional results and that the longer the preoperative waiting period, the higher the poor results.

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RESEARCH ARTICLE

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Pathology, Classification, Clinical Manifestations and Prognosis of Langerhan's Cell Histiocytosis: A Single Center Experience

ABSTRACT

Objective: The aim of the study is to raise awareness about clinical features, histopathological and radiological analyzes and treatment details of this rare disease.

Methods: A total of 55 Langerhans cell histiocytosis patients, diagnosed between the year 2006 and October 2020 in our department were included in the study. The patients were evaluated in terms of age, gender, tumor localization, risk groups, treatment modalities, recurrence, and outcome of the disease.

Results: Twenty-three out of 55 patients were children and 32 were adults. The ages of the patients were between 7 months and 72 years. Thirty-seven of the cases were male and 18 were female. The most common clinical complaint in both groups was pain and swelling. The duration between the onset of the patient complaints and admission to the hospital varies between 7 days-12 months in children, and 10 days-23 years in adults. Forty-three of the cases had single organ involvement and 12 had multiorgan involvement. The most frequently affected organ in both groups was bone. Forty of the 55 patients had follow-up data and the treatment modalities are as follows: Nine patients radiotherapy, 8 patients chemotherapy+steroid, 7 patients chemotherapy, 2 patients chemotherapy+radiotherapy+steroid, 1 patient steroid, 2 patients chemotherapy+radiotherapy. Eleven patients were followed up without additional treatment after surgery. Median follow-up from the time of biopsy was 45.9 months in children and 41.9 months in adults.

Conclusions: As a result, diagnosis requires a high degree of suspicion and final diagnosis is based on the histological examination of the lesions and biopsies.

Keywords: Langerhans Cell Histiocytosis, Adult, Pathology, Children, Prognosis.

Langerhans Hücreli Histiyositozun Patolojisi, Sınıflandırılması, Klinik Belirtileri ve Prognozu: Tek Merkez Deneyimi

ÖZET

Amaç: Çalışmanın amacı, nadir görülen bu hastalığın; klinik özellikler, histopatolojik, radyolojik analizler ve tedavi detayları hakkında farkındalığı arttırmaktır.

Gereç ve Yöntem: 2006 Ocak-2020 Ekim tarihleri arasında anabilim dalımızda tanı konan 55 Langerhans hücre histiyositozu hastası çalışmaya dahil edildi. Hastalar yaş, cinsiyet, lokalizasyon, risk grupları, tıbbi tedavi, nüks ve hastalığın sonuçları açısından değerlendirildi.

Bulgular: 55 hastanın 23'ü çocuk, 32'si yetişkindi. Hastaların yaşları 7 ay ile 72 yıl arasında değişmektedir. Olguların 37'si erkek, 18'i kadındı. Her iki gruptada en sık şikâyet ağrı ve şişlikti. Hasta şikâyeti ile hastaneye başvuru süresi çocuklarda 7 gün ile 12 ay arasında değişirken, erişkinlerde 10 gün ile 23 yıl arasında değişmektedir. Olguların 43'ünde tek organ tutulumu, 12'sinde multiorgan tutulumu vardı. Yetişkinlerde ve çocuklarda en sık etkilenen organ kemikti. Takipli hastalar tedavi açısından incelendiğinde: 9 olgu radyoterapi, 8 olgu kemoterapi + steroid, 7 olgu kemoterapi, 2 olgu kemoterapi + radyoterapi + steroid, 1 olgu sadece steroid, 2 olgu kemoterapi + radyoterapi ve onbir olgu ise cerrahi sonrası ek tedavi gerekmeksizin takip edildi. Biyopsiden sonra medyan takip süresi çocuklarda 45.9 ay ve erişkinlerde 41.2 ay idi..

Sonuç: Sonuç olarak tanı için yüksek derecede şüphe gerektiren hastalıkta, kesin tanı lezyonların ve biyopsilerin histolojik incelemesine dayanmaktadır.

Anahtar Kelimeler: Langerhans Hücre Histiyositozu, Erişkin, Patoloji, Çocuk, Prognoz.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a quite rare and heterogeneous disease that is characterized by the accumulation of Langerhans-type cells in various tissues (1-6). Although the disease is most commonly encountered at patients 20 years of age or under, it can be seen at any age (3,5). The etiology is not fully understood, it is still not determined whether LCH is mediated by an immunological or a neoplastic mechanism (3,5). Viral, bacteriological and genetic studies have been performed for etiology, and some forms were thought to have an infectious origin since they recover spontaneously (5). However, it is recently identified as a clonal disorder due to a mutation found on the BRAF gene (3,7,8). The discoveries led to a newer classification of histiocytic disorders and started an era of targeted therapy in LCH (7). In the study Özer et al; in 2019, that opened the door to targeted treatment studies in LCH two results were obtained (7). First, while 60% of LCH samples have the BRAF V 600E mutation, secondly LCHs demonstrated universal immunostaining of phospho - MEK and phospho-ERK regardless of BRAF status (7).

LCH frequently affects the bone, skin, bone marrow, lungs, lymph nodes, spleen, liver and pituitary gland (9-15). The clinical features of LCH have a wide spectrum. The spectrum of the disease ranges from an isolated lytic bone lesion to a fatal multisystemic disease. The definitive diagnosis is based on histopathologic and immunohistochemical examination of the tumor tissue. Langerhans cells are immunohistochemically positive for CD1a, Langerin and S100 (3,6). Histopathologically, the lesion may contain Langerhans cells with kidney-shaped nuclei, clear eosinophilic cytoplasm, irregular contours as well as eosinophils, lymphocytes, neutrophils, and plasma cells. Treatment modalities include performing surgery, chemotherapeutic agents and radiotherapy (3,4,6).

We analyzed our single center experience of patients with LCH. The aim of the study is to rise the awareness about clinical features, histopathological and radiological analyzes and treatment details of this rare disease.

MATERIAL AND METHODS

A total of 55 LCH patients diagnosed between years January 2006 and May 2020 in our department were included in the study. A 14-year electronic diagnostic data search was performed in the hospital medical data management system using the keywords ‘’ Langerhans cell histiocytosis ‘ and ‘’Eosinophilic granuloma ‘’ in the diagnostic line. As a result of screening, 55 patients diagnosed with Langerhans cell histiocytosis ' and 'Eosinophilic granuloma' were included in the study.

Medical records of patients with LCH were based on patient’s clinical records and retrospective clinical data collection. The patients were evaluated in terms of age, gender, localization, risk groups, medical treatment, recurrence and outcome of the disease. In addition to morphology, CD1a and S100 were administered immunohistochemically for all patients and clinical findings were evaluated together. Descriptive statistics for the continuous variables were presented as mean and standard deviation, while count and percentages for categorical variables.

SPSS version 21 (Chicago , IL, USA) statistical program was used for all statistical computations.

RESULTS

Twenty-three out of 55 patients (41.2 %) were children (under 16 years old) and 32 (58.2 %) were adults (18 years and above). The ages of the patients ranged from 7 months to 72 years. In the childhood group, there were 12 patients under the age of 5 years, 5 patients between the ages of 6-10 years and six patients aged 11 and over. In the adult group, there were 26 patients between the ages of 18 and 40, and 6 people over the age of 41. Median age at the diagnosis was 6.7 ± 4.5 in children and 35.6 ± 11.9 in adults. Thirty-seven (67.3%) of the cases were male and 18 (32.7%) were female. Male – female distribution specific to childhood and adult groups are as follows: 15 of the children were male and 8 were female, 22 of the adults were male and 10 were female.

Patient complaints vary according to the organs involved. Patients with pulmonary involvement admitted to the hospital with dry cough, shortness of breath, chest pain, patients with bone involvement swelling, pain and fracture, patients with skin involvement itching and wounds that do not heal, patients with sternum involvement with chest pain. Headache was the main complaint in patients with cranial bone involvement while low back pain was common in patients with vertebral involvement. Loose memory, polyuria, and polydipsia were the most commmon complaints in patients with hypothalamic involvement. The most common complaint in both groups was pain and swelling. While the duration of admission to the hospital from the onset of patient complaints varies between 7 days and 12 months in children (2 months on average) , it varies between 10 days to 23 years in adults (4 months on average, in case the patient who has had an itching for 23 years is excluded).

Five of our patients had obesity, 4 had diabetes mellitus, one had Familial Mediterranean Fever (FMF), one had a neurodegenerative disease, and one patient had additional cervical cancer (Patient characteristics are summarized in Table 1).

Table 1. Clinical characteristics of patients a child and adult

	Child	Adult		Child	Adult
Number of patients	23	32	**SS-LCH**	19	24
			Bone	18	16
Male/female ratio	15/8 (1.9)	22/10 (2.2)	Skin	1	4
			LN		2
Age at diagnosis median	7 M-16Y(6.91)	18-72 (35.6)	Lung		1
0-5 years old	12		Hypothalamus		1
6-10 years old	5		**MS-LCH**	4	8
11 years and above	6		Lung+bone	1	2
18-40 years old		26	Lung+skin	1	1
40 years and above		6	Lung+LN	1	
			Lung+bone+spleen	1	
Duration of complaints	7 D-12 M	10 D-23Y	Thymus+sinus		1
			Thyroid+skin		1
Relaps	2	6	Lung+hypothalamus		1
			Liver+bone		1
Follow of time	12-119 M	2-196 M	Liver+skin+BM		1
	Child	**Adult**		**Child**	**Adult**
Complaint			**Treatment**	19	21
Swelling	13	6	RT	4	5
Pain	7	15	CT	4	3
Cough	1	2	CT+RT	1	1
Fever+rash	2		CT+Steroid	4	4
Rash		5	CT+RT+Steroid		2
Itching		3	Steroid	1	
DI finding		1	Follow	5	6
			Without follow	4	11

CT: Chemotherapy; RT: Radiotherapy; DI: Diabetes insipidus; LN: Lymph node; SS: Single system; MS: Multisystem; D: Day; M: Month; Y: Years

Table 2. Clinical classification of langerhans cell histiocytosis (LCH)

Categories of LCH	Definitions
Single system LCH (SS-LCH)	One organ/system involved (unifocal or multifocal)
	-Bone (unifocal or multifocal)
	-Lymph node
	-Skin
	-Lungs
	-other (eg, thyroid, thymus, …..)
Multisystem LCH (MS-LCH)	*Two or more organs/systems
	İnvolved either with or without
	involvement of **high** risk organs

* high-risk organs include the hematologic system, the spleen and the liver LCH: Langerhans cell histiocytosis

Criteria for histological diagnosis were based on the recommendations of the Histiocyte Society (Table 2) (4,6). Forty-three of the cases had single organ involvement and 12 had multiorgan involvement (Table 3). While 19 (82.6%) of 23 patients in childhood group had single organ involvement, 4 (17.4%) patients had multiorgan involvement, 24 (75%) of 32 patients in the adult group had single organ involvement while 8 (25%) adult patients had multiorgan involvement.

Table 3. Organs involvement as single and multisystem

Held Organ	N(%)	Held Organ	N(%)
MS-LCH	12 (21.8 %)	SS-LCH	43 (78.2 %)
Lung + Bone	3 (5.5 %)	Bone	34 (61.8 %)
Lung + Skin	2 (3.7 %)	Skin	5 (9.1 %)
Liver + Bone	1 (1.8 %)	LN	2 (3.7 %)
Lung + LN	1 (1.8 %)	Lung	1 (1.8 %)
Lung + Hypothalamus	1 (1.8 %)	Hypothalamus	1 (1.8 %)
Thyroid + Skin	1 (1.8 %)		
Thymus + Sinus	1 (1.8 %)		
Lung +Spleen +Bone	1 (1.8 %)	Total	55 (100 %)
Liver+Skin+Bone morrow	1 (1.8 %)		

MS-LCH: Multi system langerhans cell histiocytosis SS-LCH: Single system langerhans cell histiocytosis LN: Lymph node

In childhood group three of the patients with single organ involvement had multifocal bone involvement. In adults five of the cases with single organ involvement were also multifocal. In three patients multifocally involved organs were skin and in the remaining two were lymph nodes. The organ

most frequently affected organ both in adults and children was the bone. The most frequently involved bones were cranial bones. The numbers of organs involved in our series are summarized in Table 4. Of the 55 cases, 54 (98.2%) were alive, 1 (1.8%) were dead. All patients except one were still in complete remission at the time of the study review.

Table 4. The numbers of organs held in our series

Involvement organs	N	Involvement organs	N
Bone	39	Skin	9
Head bone	19	Lung	8
Vertebrae	8	Lymph node	3
Humerus	4	Liver	2
Sternum	3	Hypothalamus	2
Femur	2	Thymus	1
Scapula	1	Spleen	1
Clavicula	1	Thyroid	1
Radius	1	Bone morrow	1

Nineteen (82.6%) of 23 child patients, and 21 (65.6%) of 32 adult patients had follow-up data. Out of the 15 cases without follow-up data, 8 were consultation cases that admitted to our hospital for pathologic diagnosis confirmation, 5 cases did not re-admitted to our hospital after the diagnosis and two cases were lost from the follow-up after 3 and 5 months, respectively.

The treatment modalities of the 40 patients who had follow-up data are as follows: Nine patients radiotherapy (RT), 8 patients chemotherapy (CT) + steroid, 7 patients CT, 2 patients CT + RT + steroid, 1 patient steroid, 2 patients CT + RT. Eleven patients were followed up without additional treatment after surgery.

Median follow up from of biopsy was 45.9 ± 30.2 months (range= 12-119 months) in children and 41.9 ± 52.6 months (range= 2-176 months) in adults.

Recurrence was observed in 8 patients. Two of the recurrent cases were children and 6 were adults. Recurrences in children both occurred after 1 year, while recurrences occurred after 7 months, 1, 3, 7, 8, and 10 years respectively in adults. The characteristics of patients with recurrent diseases are summarized in the table (Table 5). The first recurrence of our case (176 months), which we followed for the longest period in adults, is 7 years later. The patient then repeated three more times but is now being followed in remission. The patient with died was 35 years old male and had multiorgan (liver + skin + bone marrow) involvement. The patient was diagnosed as ready paraffin blocks (liver + bone marrow) and then was out of follow-up.

Table 5. Features of our recurrence cases

Case	Age	Gender	Localization	Multifocal	Recurrence
1	2	Female	Lung+bone+spleen	No	1 year
2	3	Male	Bone (Cranium)	No	1 year
3	25	Female	Lung +skin	No	10 year
4	32	Female	Lymph node	Yes	8 year
5	35	Male	Bone (Cranium)	No	7 month
6	27	Male	Thyroid + skin	No	7 year
7	27	Male	Lymph node	Yes	1 year
8	33	Female	Skin	No	3 year

DISCUSSION

Although LCH previously thought as a reactive process in which the Langerhans-type cell accumulate in various tissues and cause damage , it is now classified as a true neoplasm due to BRAF V600 mutations recently defined in these lesions (5,11). LCH is a rare disease and can occur at any age, particularly in younger children. The majority of reported cases (60-70%) are under 20 years old. The most common age range is between 5-10 years old. Adult pateints are predominant in our series; 32 (58.2%) of our cases were adults and 23 (41.2%) were children. About half of our pediatric patients were between 0-5 years old. LCH is slightly more common in men than in women (55%) (5,14). In our series there were male predominance in both age groups. The M / F ratio was 15/8 (1.9) in children, and 22/10 (2.2) in adults.

Although the disease was previously called with 4 different names; Hashimoto Pritzker disease, Eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease, representing the 4 different clinical presentations, these diseases are now all called as LCH due to their common immunological properties (2,5,13,16).

Etiology of the disease is still not determined whether it is mediated by on immunological or a neoplastic mechanism. It is however recognized as a clonal disorder and a mutation of the BRAF gene (BRAF V600) has been lately identified present in more than half of the patients, favoring the hypothesis of a neoplastic origin (1,3,7,8,14).

The disease has no specific symptoms, physical examination, or laboratory findings. The diagnosis of the disease is made by clinical, histopathological and immunohistochemical analysis. It should be considered in patients with unexplained clinical manifestations of skin, bone, ear, lymph node, lung, liver and CNS. LCH can be asymptomatic or it can manifest with different signs or symptoms according to the organ involved. The most common symptoms are pain, bone swelling, cutaneous rash, and lymphadenopathy, followed by respiratory insufficiency, hepatomegaly, splenomegaly, neutropenia, anemia (5,17). The most common complaints in our series were pain and bone

swelling. The median time for the start of the complaints and admission to the hospital was 2 months (7 days-12 months) in children and 4 months (10 days-23 years) in adults, in our series. In the literature, the median time from the first symptom to diagnosis was reported as 1-1.5 months (6). The reason for the high prevalence of adult patients in our series may be that patients are asymptomatic and undiagnosed for a longer period of time.

The diagnosis of LCH is often difficult and delayed (9). Due to the complaints of swelling and pain in bone involvement, the duration of diagnosis is shorter as the time to admission to the hospital is shorter. In skin involvement and/or other organ involvements, if the disease is suspected and a biopsy is taken, the diagnosis time may be shortened.

Radiological imaging methods are also used in diagnosis. In particular, findings in bone involvement imitate many bone tumors radiologically (such as Ewing sarcoma, aneurysmal bone cyst, osteomyelitis, osteosarcoma, metastatic bone tumor). In our series, Ewing sarcoma and osteomyelitis are frequently considered in the radiological differential diagnosis of the bone lesions. The definitive diagnosis is based on the histopathologic and immunohistochemical examination of tumor tissue (6,17). Diagnosis was established for all of our patients by demonstrating pathologic Langerhans cells which are stained immunohistochemically with CD1a and S100 as well as typical clinical findings (6,10,11). Histopathologically, eosinophils, neutrophils, lymphocytes and plasma cells can also accompany Langerhans cell proliferation (Figure 1). In all of our cases, S100 (Figure 2) and CD1a (Figure 3) were positive in langerhans cells.

In the classification made by the LCH study group according to organ involvement, the disease is examined in two main groups: single system (SS) involvement and multisystem (MS) involvement (4,6). While single organ involvement (monofocal or monostatic type) of the disease constitutes 65% of cases, 35% of cases show multiorgan involvement (5). In our series, 43 (78.2%) cases, (19 in children and 24 in adults) showed single organ involvement. Four of the 12 patient (22.8%) with multiorgan involvement were children and eight were adults. A disease that starts as the monostatic type can then turn into the polistatic type.

Bone involvement with or without other associated sites are the most common manifestation of LCH and has been observed in 80-100% of cases based on a review of the literature (9). The single organ involved is most commonly the bone, which is followed by skin (11). The organ involvement pattern (bone being the most common, and skin the second) in our series is consistent with this literature. LCH can involve any bone of the body. The most commonly involved bones in our cases are cranium and vertebrae and it is also compatible with the literature. Unusual sites of bone involvement includes zygomatic bone, scapula, clavicula and sternum.

In children common sites of bone involvement include craniofasial bones, femur, ribs, vertebrae and humerus (4,6). Bone involvement was present in 39 (70.9%) of our patients. Involved bones were craniofacial bones 19 (34.6%), vertebrae 8 (14.5%), sternum 3 (5.5%) , scapula 1 (1.8%), clavicule 1 (1.8%), and long bones including femur, humerus, radius 7 (12.7%).

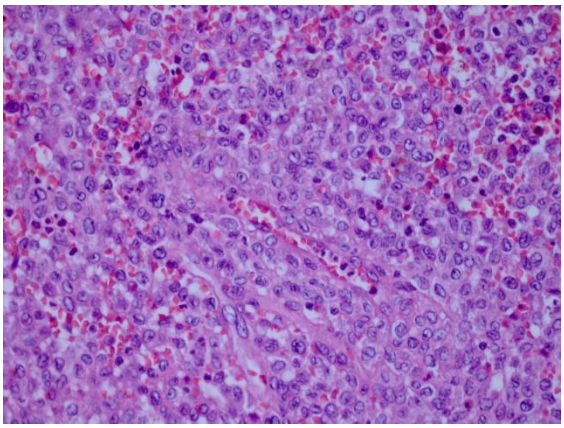

Figure 1. Close-up view of langerhans cells with irregular contours, some with kidney-shaped nuclei, clear-eosinophilic cytoplasm (HEx200)

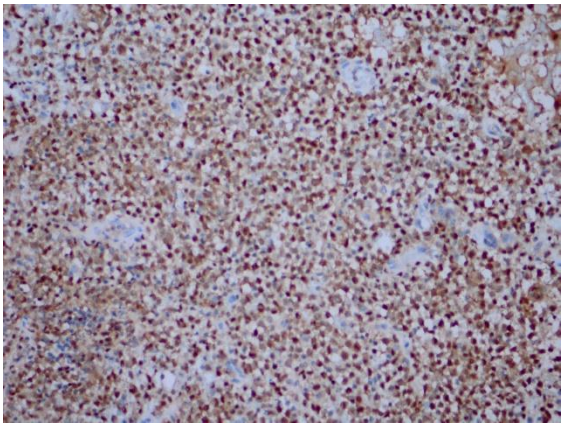

Figure 2. Diffuse positivity of Langerhans cells with S100 (IHKx200)

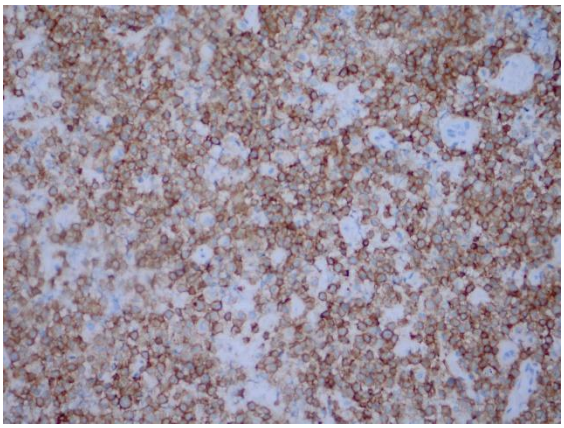

Figure 3. Diffuse positivity of langerhans cells with CD1a (IHKx200)

In considering patients of all ages, skin is the second most frequently involved organ system after bone (18). Skin involvement had been reported in over one third (20-38%) of children with LCH (6). Skin involvement can be a limited disease or a component of MS-LCH. Isolated cutaneous disease has only been observed in 2% of the total LCH (20). Skin involvement was present in 9 (16.4%) of our cases, and 5 of them had skin limited disease. Skin involvement was present in 2 children (1 SS-LCH, 1 MS-LCH) and 7 adults (4 SS-LCH, 3 MS-LCH). Especially in infants, a seborrheic dermatitis-like rash often causes LCH to be misdiagnosed as seborrheic dermatitis, while groin involvement can present as treatment-resistant, recurring diaper dermatitis (18). In our series, three cases were followed up with seborrheic dermatitis and were subsequently diagnosed as a result of a biopsy. In two of our cases (7 months and 1 year old), LCH was diagnosed as a result of biopsies taken for persistent lesions in the perianal region.

Pulmonary involvement is observed in 3-5% of patients with LCH. While in adult LCH, pulmonary involvement is as high as 50-60% compared to other organs, unlike the pulmonary LCH where pulmonary involvement is rare (6). In our series, there was a total of 8 patients have pulmonary involvement, which of 3 are children and 5 are adults. Isolated type pulmonary disease occurs predominantly in adults, whereas this is rare in children (19). In our series, there was no case with isolated pulmonary in children, and all 3 pediatric patients pulmonary involvement was a component of systemic disease. In adults, isolated pulmonary disease is observed in 1 patient, and lung involvement in remaining 4 patients was observed as a component of multiorgan involvement. Five of the patients with lung involvement were male and 3 were female. In our series, lung involvement is observed less frequently than in the literature. The rate of lung involvement in 14.5% in our series, while it is 22-24 % in the literature (6). Cigarette smoking is reported in an overwhelming majority of adult patients with pulmonary involvement (10,19,20). Ten of our patients were smokers, and four of them had lung involvement. The reason for the low lung involvement rate in our series may be due to the low rate of smoking among our patients.

Central nervous system (CNS) involvement usually occurs by contiguity of the skull lesions into the brain tissue. Most commonly involved sites are the cerebellum, hypothalamic nuclei and pituitary gland, producing diabetes insipidus (3). Diabetes insipitus (DI) is the most common endocrinopathy in LCH (16). DI prevalence has a very broad range in various studies, changing between 5-50% pointing out the risk of progressive disease (2). Two of our patients had hypothalamic involvement and presented DI findings. One of these patients was a child and the other one was an adult. Thyroid involvement is quite rare, with only 75 cases reported in the literature and may present with nodular or diffuse enlargement (18,21). Patients are typically euthyroid or hypothyroid (18). In our series, Thyroid + skin involvement was present in one case. Our patient had subclinical hypothyroidism and the LCH lesion in the thyroid was growing nodularly.

Liver involvement is especially seen in patients with MS-LCH (18,22). Patients may present with hepatomegaly, jaundice or sclerosing cholangitis (18). There was liver involvement in two cases with multisystem involvement in our series. While one of the cases presented with the complaint of pain and multiple liver masses, the other admitted to the clinic with the complaint of itching and jaundice lasting for about 20 months. In the histopathological evaluation of the biopsy performed to enlighten the etiology of itching and jaundice in this patients, langerhans cell infiltration, as well as grade 4-5 fibrosis were observed. In long-term and resistant itching and patients with unexplained jaundice, LCH should be considered and biopsy should be performed for differential diagnosis.

Thymus involvement is mostly seen in patients with MS-LCH. Isolated LCH of the thymus gland is quite rare (23,24). There was thymus involvement in one case with multisystem involvement in our series.

Addition of skin and mucousal lesions to the bone lesions, relapse of bone lesions after treatment, involvement of three or more bones, patients age under 5 years, and two or more system involvements accompanying to bone lesions are signs of poor prognosis (5). Previous studies on LCH have shown that children do worse than adults (2). In our series, 1 case died and 8 cases had relapsed. Our patient who died was a 35 years old male and had MS-LCH (Liver + bone marrow + skin). Two of our recurrent patients were children and 6 were adults. One of the relapsed children had multiorgan involvement (Bone + lung + spleen) and the other case had multiple bone involvement. Both patients were under 5 years old. Two of the 6 patients who relapsed in adult age group were MS-LCH and 4 were SS-LCH. Two of the patients with SS-LCH had multifocal involvement. In our patients with died and recurrence were present organs involvement which were risk groups (bone morrow, spleen, and liver).

The course of the disease varies from spontaneous resolution to a progressive multisystem disorder with organ dysfunction and potentially life-threatening complications (9). In the treatment of LCH, if the lesion does not show any symptoms, it should only be monitored, even if it is massive. However, if there are findings such as pain, deformity, risk of pathological fracture, neurological deficit, it should be treated.

Differential diagnosis includes indeterminate dendritic cell tumor (IDCT) and Langerhans cell sarcoma (LCS). IDCTs are Langerin negative, while LCS and LCH are positive. IDCT usually shows

aggressive histological features (such as central necrosis and a high Ki67 proliferation index). In addition, Birbeck granules are not observed in electron microscopy (25,26). Cytologically LCS can be differentiated from LCH as it displays malignant features (such as cellular atypia, increased mitotic activity, and necrosis) (27).

In treatment, steroid application into the lesion as well as curettage and bone graft, CT, low dose RT, combined therapies, and bone marrow transplantation can be applied (3,5). In localized disease, namely in unifocal bone lesions, surgical curettage should be considered as a first-line therapeutic option, as well as intralesional steroids or focal RT. Chemotherapy is indicated in multisystem disease or high-risk organ involvement (3). The treatment method is determined by the age of the patient, the localization of the lesion, the number of bone and lesions retained, the size of the lesion, and its natural course. Patients with a multisystem disease or multifocal bone lesions are usually treated with systemic CT (1). When we look at the treatment protocols of our 40 patients who had follow-up data in our series: 11 were followed, 9 were treated with RT, 8 were treated with CT + steroid, 7 were treated with CT, 2 were treated with CT + RT + steroid, and 1 had only steroid treatment. Since the RT dose used in the treatment of LCH is low and effective, side effects can be well tolerated (2). In our series, no secondary cancers or treatment related serious late effects were developed so far. Evaluations were done with 3-6 months of intervals during treatment and until 3-5 years after the end of treatment, and whenever patients complained of systems relevant to LCH. In our series, while the follow-up of pediatric patients was more regular, follow-up intervals were remarkably longer in the adult age group. The reason for the relapse rate in children (10.1%) to be lower than adults (28.5%) may be due to their regular follow-up.

The limitation of our study is that it is retrospective and not supported molecularly (such as BRAF). Our study should be supported by prospective studies.

Consequently; Diagnosis of LCH requires a clinically high degree of suspicion and the final diagnosis is usually based on the histopathological examination of the lesions. LCH disease should be considered in the differential diagnosis in patients presenting with bone pain, prolonged and resistant itching, prolonged cough, or unexplained jaundice. Multidisciplinary optimized therapeutic approaches are needed for better management of these patients. Identification of patients with high-risk organ involvement is essential because these patients usually need more aggressive treatment. We believe that correct and early diagnosis is a factor prognostically as important as multisystem involvement. We wanted to draw attention to the fact that this disease, which has a good prognosis with correct diagnosis, proper management and regular follow up, may well be seen in adults , not only in children, and should be kept in mind in the differantial diagnosis.

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