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ORIGINAL ARTICLE

Emergency Medical Technician Professional Competence Perception Scale: Validity and Reliability Study

Acil Tıp Teknikeri Mesleki Yeterlik Algı Ölçeği: Geçerlik ve Güvenirlik Çalışması

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ABSTRACT

The objective of this study was to develop a reliable and valid instrument to assess the professional competence of emergency medical technicians. The research sampling consists of 820 students who were in their last year of the First and Emergency Aid Program. The tools utilized for data collection included a Demographic Information Form, the Emergency Medical Technician Professional Competence Perception Scale (EMT-PCPS), and the Self-Efficacy-Competence Scale. To test the validity of the measuring tool's structure, exploratory factor analysis (EFA), item analysis and confirmatory factor analysis (CFA) were used. Cronbach Alpha coefficients and test-retest results have been examined for reliability testing. According to the validity test results, the 4-factor structure of EMT-PCPS explains 70.45% of the total variance. According to the reliability analysis results, the item-total test correlation values were greater than .30, the Cronbach's alpha coefficient was .97, and the correlation values between test-retest scores were medium to good ($p<.01$). The research found that the EMT-PCPS is a valid and reliable measuring instrument for analyzing the professional competence perception levels of Emergency Medical Technicians who are candidates to keep working in the profession.

Keywords: Emergency medicine technician; Professional competence perception; Scale development; Paramedic

ÖZ

Araştırmada, Acil Tıp Teknikerlerinin mesleki yeterlik algılarını inceleyebilmek amacıyla geçerli ve güvenilir bir ölçüm aracının geliştirilmesi amaçlanmıştır. Araştırmanın örneklemini İlk ve Acil Yardım Programı son sınıfta öğrenim gören toplam 820 öğrenci oluşturmaktadır. Verilerin toplanmasında, Demografik Bilgi Formu, Acil Tıp Teknikeri Mesleki Yeterlik Algı Ölçeği (ATT-MYAÖ) ve Öz-Etkililik-Yeterlik Ölçeği kullanılmıştır. Ölçme aracının yapı geçerliğini sınamak için Açıklayıcı Faktör Analizi (AFA), Madde Analizi ve Doğrulayıcı Faktör Analizi (DFA) uygulanmıştır. Güvenirlik sınamaları için Cronbach Alpha katsayısı ve test-tekrar test bulguları incelenmiştir. Geçerlik sınamalarında elde edilen bulgulara göre; ATT-MYAÖ'nün 4 faktörlü yapısı, toplam varyansın %70.45'ini açıklamaktadır. Güvenirlik analizleri bulgularına göre ise Madde-toplam test korelasyon değerlerinin .30 üzerinde, Cronbach alfa katsayısının .97 ve test-tekrar test puanları arasındaki korelasyon değerlerinin orta ve iyi düzeyde olduğu tespit edilmiştir ($p<.01$). Araştırma sonucunda, ATT-MYAÖ'nin, mesleği sürdürmeye aday Acil Tıp Teknikerlerinin mesleki yeterlik algı düzeylerini incelemede geçerli ve güvenilir bir ölçüm aracı olduğu belirlenmiştir.

Anahtar Sözcükler: Acil tıp teknikeri; Mesleki yeterlik algısı; Ölçek geliştirme, Paramedik

Introduction

In many countries, emergency health services are given in order to reduce the patient's or injured person's mortality, disease, and social consequences in the event of a sudden illness or accidental injury. When emergency medical intervention is required, healthcare professionals must instigate swift and accurate responses. Consequently, those involved in the delivery of emergency health services should have specialized training in emergency care and treatment. As the proportion of Emergency Medical Technicians working in the pre-hospital area and hospital emergency services in emergency health services has led to an increase in their roles and responsibilities parellel to the development of medicine, and the level of clinical competence expected from Emergency Medical Technicians has also increased. Therefore, practicing and aspirant EMTs must possess requisite skills and competencies, as well as an adequate belief in their abilities to perform potential life-saving procedures in order to succeed in their profession and fulfill their professional obligations (1). "Competence" is described (2) as "the state of being sufficient, the specialist knowledge providing the power to perform a job, competence, and the ability to fulfill one's duty. " Self-efficacy is explained by Bandura as an individual's assessment of their own perceived ability in a specific field (context), emphasizing that the belief system of efficacy is not a global trait, but a set of distinct self-beliefs related to diverse functional areas (3,4). In the literature, research on competence focuses on the concept of self-efficacy and there appears to be relationship between academic success, psychological

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well-being, problem solving, clinical competence, clinical performance and self-efficacy and the concept of self-efficacy being the subject of research across different fields (such as health, psychology, education) (5-9).

Research exploring the self-efficacy levels of students in the First and Emergency Aid Program have identified a correlation between the students' application of theoretical knowledge in practice and their competence perceptions, with these perceptions differing based on whether they were practicing or not (10,11). In the literature, studies examining the self-efficacy of EMTs and the relationship between self-efficacy and various factors generally adopt assessment tools prepared as task-specific checklists. However, there is no valid and reliable measurement tool available to examine perceptions of professional competence, which includes a comprehensive view of roles, authorities, and responsibilities (12-15).

This study, therefore, aimed to develop a measurement instrument to examine the perception of professional competence levels among EMTs.

Method

Study Group and Research Model

This methodological and descriptive study was conducted on a sample of 820 students in their final year at the Health Services Vocational School First and Emergency Aid Program during the spring semester of the 2021-2022 academic year. Information regarding the sampling process is shown in Figure 1.

Data Collection Tools

We employed the Demographic Information Form, the Emergency Medical Technician Professional Competence Perception Scale (EMT-PCPS), and the Self-Efficacy-Competence Scale to collect the data.

Emergency Medical Technician Professional Competence Perception Scale (EMT-PCPS)

The researcher devised a study aimed at investigating the professional competence perceptions of emergency medical technicians. In the light of the scope of the research, statements related to these perceptions were defined, informed by the duties, authorities, and responsibilities outlined in the regulation and supported by a thorough examination of pertinent literature. This led to the creation of an item pool (10-11; 16-21). Field experts evaluated the assembled item pool via face-to-face interviews, which culminated in a 119-item draft scale form. This form was then submitted to 15 experts from the fields of Health Sciences and Educational Sciences for evaluation of its language and content validity. A 3-point scale (1 - Inappropriate, remove the item; 2 - Somewhat appropriate, modify as suggested; 3 - Appropriate, use as is) was used to gather expert opinions.

The Lawshe Technique was applied to evaluate the expert opinions. Post-evaluation, 7 items with negative Content Validity Ratio (CVR) values were eliminated from the draft scale. To ascertain the significance of the positive CVR value items, the minimum CVR values at a=.05 level of significance were compared with the table values of the Content Validity Criterion (CVR) proposed by Ayre and Scally (2014) (CVR critical value =.60 for 15 experts). Following this comparison, 5 items that fell below the critical value were removed from the draft scale (22). The Content Validity Index (CVI) for the entire scale was calculated by averaging the CVI values of the remaining 107 items, resulting in a CVI of .93, which surpasses the set benchmark of .60 (CVI>CVI), indicating that the content validity of the draft scale was statistically significant. In line with the opinions of the Turkish Language Expert and field experts, the draft scale form, in which 21 items were revised to increase comprehensibility in terms of language and expression and comprising solely of positive statements, was converted into 7-point Likert type ((1) Strongly disagree.... (4) Undecided/No opinion.... (7) Strongly agree). This revised form consist of 107 items.

To assess the comprehensibility of the draft scale items, their ability to express the same meaning consistently across all participants, and the duration of the application, a pilot study was conducted with 36 students who were not included in the sample. The pilot study resulted in the removal of 29 items due to their lengthy implementation time and similarity in expression with other items on the scale. This decision was informed by the feedback of 6 initial evaluators and 2 field experts. Certain items were also reformulated as separate items as they questioned different skill levels of competence perception. Two new items concerning "normal newborn care and emergency care in birth complications" were added to the draft scale, and certain items were revised for better comprehensibility.

The revised scale, with a recalculated CVI of .94, demonstrated statistically significant content validity (CVI=.94>CVI=.75). The psychometric evaluation of the draft scale was then conducted on 81 items in a larger sample group.

Self-Efficacy-Competence Scale

The criterion validity of the EMT-PCPS scores was examined by implementing the Self-Efficacy-Competence Scale, a 5-point Likert-type scale adapted into Turkish by Gözüm and Aksayan (1999). This scale, consisting of 4 sub-dimensions and 23 items, scored 14 items in the opposite direction, with the total scale scores varying between 23 and 115. An increase in total score signifies a high level of an individual's self-efficacy-competence perception (23). The Cronbach's alpha value of the scale in this study was found as .85.

Data Analysis

IBM SPSS Statistics 26.0 and AMOS 24.0 licensed software were utilized to analyze the research data. Exploratory Factor Analysis (EFA), Confirmatory Factor

Analysis (CFA), and item analysis were used in the study to examine the construct validity of the scale. Pearson correlation analysis was utilized to test the criterion validity of the scale. The Cronbach Alpha internal consistency coefficient was calculated as part of the reliability studies, the test-retest method was employed to test the scale's stability, and the link between the two applications was examined using the Intraclass Correlation Coefficient (ICC).

Ethics of the Study

Ethics committee approval (dated 31.12.2021, numbered 2021/1087, and dated 30.12.2022, numbered 2022/1210) was obtained from Ondokuz Mayıs University Social and Human Sciences Research Ethics Committee. Research permissions were also procured from the institutions where the research was carried out, and permission was secured to use the Self-Efficacy-Competence Scale. The purpose of the research was explained to the senior students of the First and Emergency Aid Program, ensuring that the research data would not be used for any other purpose, and verbal and written consents were obtained from the students.

Results

This section presents the findings of the statistical analysis conducted to ascertain the validity and reliability of the EMT-PCPS.

Construct Validity

Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) were carried out to assess the construct validity of the measures obtained from the EMT-PCPS.

The appropriateness of EFA was evaluated by the Kaiser-Meyer-Olkin (KMO) coefficient and Bartlett's Sphericity test (n=400). The KMO value, which indicates the suitability of the sample size and the correlation between the items for factor analysis, is deemed sufficient when it is .60 and above, and excellent when it is .90 and above (24). In this study, the KMO sample suitability value was .98. Bartlett's Test of Sphericity was employed to test the assumption of the similarity of the correlation matrix (25). The chi-square test statistic was significant [$\chi2=31508.30$, $p<.001$)], indicating the data stemmed from a multivariate normal distribution. These findings demonstrate that the study data are appropriate for factor analysis.

Exploratory Factor Analysis (EFA)

EFA was undertaken using data acquired from 400 participants. To determine the factor structure of the draft scale, a principal component analysis with Varimax rotation was utilized. The acceptable loading level for the scale items was established as above .40 (26).

During the first stage, it was discerned that the draft scale was consolidated under 4 factors, accounting for 69.44% of the total variance. Post-EFA, there were no items with factor loadings below .40, but 9 items with loadings close to multiple factors (below 10%) were eliminated from the draft scale.

In the second stage, with the application of EFA and Varimax rotation on the 72-item version of the scale, the draft scale was seen to congregate under 4 factors, explaining 70.07% of the total variance. Here, 4 items with loadings close to multiple factors were discarded from the draft scale.

Subsequently, in the third stage, the 68-item version of the scale underwent EFA and Varimax rotation. The result indicated that the draft scale was assembled under 4 factors, explaining 70.31% of the total variance, and 2 items with loadings close to multiple factors were purged from the draft scale.

In the fourth and final stage, when EFA and Varimax rotation were applied to the 66-item version of the scale, no items displayed a factor loading below .40 or loadings close to multiple factors.

Thus, it was found that the 66 items in the scale were divided into 4 sub-dimensions, which expounded 70.45% of the total variance. The factor loadings ranged between .46 and .79. Additionally, no items with an anti-image correlation value below .50 were detected in the draft scale form. The factor weights related to the exploratory factor analysis of the EMT-PCPS are delineated in Table 1.

Table 2 discloses that the 4-factor structure elucidated 70.45% of the total variance of the draft scale. The eigenvalues for each sub-dimension were observed as Factor 1: 15.37, Factor 2: 11.72, Factor 3: 11.70, Factor 4: 7.71, respectively. Upon analyzing the content of the items collated under these factors, the dimensions were christened as "Professional Role and Responsibility (Factor 1)", "Patient/Injured Handling and Equipment Use (Factor 2)", "Clinical Decision Making and Practice (Factor 3)", and "Patient/Injured Assessment (Factor 4)".

Confirmatory Factor Analysis (CFA)

The construct validity of the draft scale was examined via a CFA utilizing data from 356 participants, with the intention to validate the structure developed by EFA. Post-CFA, 'item 8', which had a standardized factor loading below .40, was eliminated from the scale and CFA was re-conducted with 65 items. The standardized factor loadings of the items constituting the four sub-dimensions of the EMT-PCPS, resulting from the repeated CFA, are illustrated in Table 3.

To verify the model obtained via CFA, fit criteria (comprising of goodness of fit indices and corrected Chi-square (κ^2/df) value) were computed for the factors present in the model (Table 4). Upon examining the model results in Table 4, the RMSEA fit criterion is .05, indicating an acceptable fit. The additional fit criteria, IFI and SRMR, also signify an acceptable fit. The acceptable fit of the fit criteria, along with the good fit of the adjusted chi-square value, demonstrates that our data exhibit an acceptable fit. Consequently, our model is statistically significant and valid ($p=.001$; $p<.01$).

Analyzing the correlations between the factor scores

in Table 5 reveals a positive, moderate, and strong relationship between the factors, which is statistically significant (p=.001; p<.01). Furthermore, the correlation coefficients of the four factors in the scale with each other were found to exceed .30.

Item Analyses

Item analyses were avaluated with the data of 356 participants in the CFA group, by calculating the item-total test correlation and comparing the 27% lower-upper groups.

In the study, item-total test correlation values ranged from 0.44 to 0.75, and t values in t-test findings indicating the significance of the difference between the item scores of the upper 27% and lower 27% groups ranged from 5.655 to 14.557 (p<.01). Additionally, when examining the Cronbach's alpha values upon deletion of the item, it was discerned that the exclusion of any item from the factor would not enhance reliability.

Criterion Dependent Validity

In addition to the previously summarized structural evidence of the EMT-PCPS, the correlation coefficient between the scale and the Self-Efficacy-Competence Scale was calculated for criterion validity (n=356). It was found that there was a statistically significantly positive, weak, and very weak correlation between the participants' scores on the total Self-Efficacy-Competence Scale and their scores on the EMT-PCPS subscales and the total scale (Table 6).

Internal Consistency Reliability

To provide evidence for the reliability of the measurement tool, Cronbach's alpha internal consistency coefficient for the overall scale and its sub-dimensions was calculated with the data of the participants in the CFA group (n=356) (Table 7).

When Cronbach's alpha values are examined in Table 7, it is .95 for Professional Role and Responsibility sub-dimension; .96 for the Patient/Injured Transportation and Equipment Use sub-dimension; .94 for Clinical Decision Making and Practice sub-dimension; and .92 for Patient/Injured Assessment sub-dimension. Cronbach's alpha value for the total EMT-PCPS was .97.

Test-Retest Reliability

The temporal stability of the EMT-PCPS was evaluated by examining the relationship between the scores obtained from the initial and subsequent administrations using the intra-class correlation coefficient (ICC) (Table 8).

Upon investigating the ICC levels between the scores obtained by the participants in the test-retest from the EMT-PCPS sub-dimensions and the total scale (as presented in Table 8), a statistically moderate to good level of agreement was discerned (ICC=.60, .67, .54, .63, .75; p<.01). Moreover, a dependent sample t-test was employed to determine if there was a disparity between the mean scores derived from the first and second administrations. It was observed that the change in participants' EMT-PCPS sub-dimension and total scale scores did not present a statistically significant difference (p>.05).

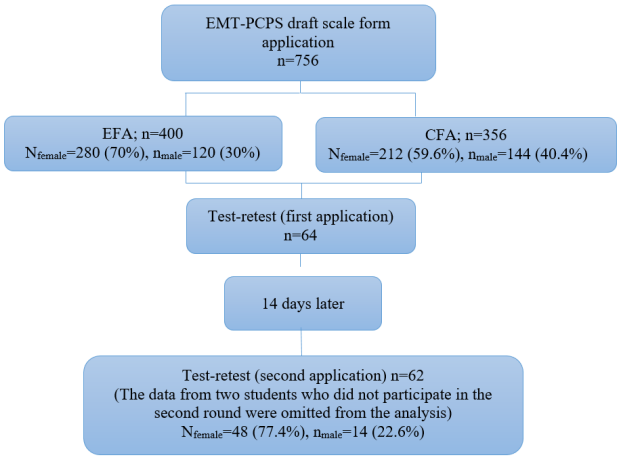

Figure 1. Study Group and Research Model

Table 1. Factor loading values as a result of exploratory factor analysis of EMT-PCPS (n=400)

Factor	EMT-	Standardized Factor Load	Factor	EMT-	Standardized Factor Load
Factor 1	PCPS16	.72	Factor 2	PCPS74	.75
	PCPS19	.72		PCPS76	.74
	PCPS5	.72		PCPS77	.73
	PCPS18	.72		PCPS78	.73
	PCPS17	.71		PCPS75	.72
	PCPS9	.71		PCPS71	.72
	PCPS3	.71		PCPS73	.71
	PCPS13	.71		PCPS72	.70
	PCPS22	.71		PCPS70	.70
	PCPS15	.70		PCPS79	.69
	PCPS2	.70		PCPS80	.66
	PCPS21	.69		PCPS81	.62
	PCPS14	.69		PCPS66	.59
	PCPS20	.68		PCPS68	.59
	PCPS7	.68		PCPS67	.59
	PCPS12	.66		PCPS65	.58
	PCPS6	.64	Factor 3	PCPS55	.79
	PCPS11	.64		PCPS50	.78
	PCPS1	.63		PCPS62	.74
	PCPS4	.62		PCPS54	.73
	PCPS10	.58		PCPS60	.73
	PCPS8	.46		PCPS48	.72
Factor 4	PCPS44	.65		PCPS63	.71
	PCPS30	.64		PCPS49	.70
	PCPS43	.63		PCPS61	.69
	PCPS28	.62		PCPS42	.69
	PCPS33	.62		PCPS52	.63
	PCPS32	.60		PCPS53	.61
	PCPS29	.60		PCPS46	.57
	PCPS31	.60		PCPS47	.57
	PCPS27	.56		PCPS35	.54
	PCPS26	.51		PCPS39	.53
				PCPS45	.52
				PCPS34	.51

EMT-PCPS: Emergency Medical Technician Professional Competence Perception Scale.

Table 2. Eigenvalues and explained variance results of EMT-PCPS factor analysis (n=400)

	Eigenvalues	Variance %	Total Variance %
Factor 1	15.37	23.29	23.29
Factor 2	11.72	17.75	41.04
Factor 3	11.70	17.73	58.77
Factor 4	7.71	11.68	70.45

EMT-PCPS: Emergency Medical Technician Professional Competence Perception Scale.

Table 3. Factor loading values as a result of confirmatory factor analysis of EMT-PCPS (n=356)

Factor	EMT-	Standardized Factor Load	Factor	EMT-	Standardized Factor Load
Factor 1	PCPS22 (21)	.78	Factor 2	PCPS65 (50)	.72
	PCPS21 (20)	.75		PCPS66 (51)	.76
	PCPS20 (19)	.75		PCPS67 (52)	.75
	PCPS19 (18)	.83		PCPS68 (53)	.79
	PCPS18 (17)	.78		PCPS70 (54)	.78
	PCPS17 (16)	.63		PCPS71 (55)	.87
	PCPS16 (15)	.67		PCPS72 (56)	.85
	PCPS15 (14)	.74		PCPS73 (57)	.84
	PCPS14 (13)	.75		PCPS74 (58)	.82
	PCPS13 (12)	.72		PCPS75 (59)	.85
	PCPS12 (11)	.67		PCPS76 (60)	.83
	PCPS11 (10)	.60		PCPS77 (61)	.78
	PCPS10 (9)	.49		PCPS78 (62)	.82
	PCPS9 (8)	.66		PCPS79 (63)	.74
	PCPS7	.67		PCPS80 (64)	.73
	PCPS6	.66		PCPS81 (65)	.73
	PCPS5	.73	Factor 3	PCPS34 (32)	.64
	PCPS4	.54		PCPS35 (33)	.61
	PCPS3	.67		PCPS39 (34)	.65
	PCPS2	.58		PCPS42 (35)	.68
	PCPS1	.58		PCPS45 (36)	.71
Factor 4	PCPS26 (22)	.72		PCPS46 (37)	.72
	PCPS27 (23)	.65		PCPS47 (38)	.69
	PCPS28 (24)	.80		PCPS48 (39)	.75
	PCPS29 (25)	.88		PCPS49 (40)	.74
	PCPS30 (26)	.86		PCPS50 (41)	.65
	PCPS31 (27)	.82		PCPS52 (42)	.69
	PCPS32 (28)	.77		PCPS53 (43)	.73
	PCPS33 (29)	.68		PCPS54 (44)	.75
	PCPS43 (30)	.53		PCPS55 (45)	.74
	PCPS44 (31)	.65		PCPS60 (46)	.67
				PCPS61 (47)	.66
				PCPS62 (48)	.61
				PCPS63 (49)	.61

EMT-PCPS: Emergency Medical Technician Professional Competence Perception Scale.

***** As a result of CFA, revised item numbers are shown in ( ).

Table 4. Confirmatory factor analysis model data fit indices of EMT-PCPS (n=356)

Fit Indices	Good Fit	Acceptable Fit	The Results of Model	
RMSEA	0<RMSEA<.05	.05≤ RMSEA ≤.10	.05	Acceptable fit
NFI	.95≤ NFI ≤1	.90≤ NFI ≤.95	.82	
NNFI	.97≤ NNF ≤1	.95≤ NNFI ≤.97	.89	
CFI	.97≤ CFI ≤1	.95≤ CFI ≤.97	.90	
IFI	.95≤ IFI ≤1	.90≤ IFI ≤.95	.90	Acceptable fit
RFI	.90≤ RFI ≤1	.85≤ RFI ≤.90	.81	
SRMR	0≤ SRMR ≤.05	.05≤ SRMR ≤.10	.07	Acceptable fit
GFI	.95 ≤GFI ≤1	.90≤ GFI ≤.95	.75	
AGFI	.90≤ AGFI ≤1	.85≤ AGFI ≤.90	.73	
κ^2 /df (3863.059/1938)	0 ≤ κ^2/df ≤ 3	3 ≤ κ^2/df ≤ 5	1.99	Good fit

Table 5. Relationship between EMT-PCPS factors

		Factor 1	**Factor 2**	**Factor 3**	**Factor 4**
Factor 1 (Professional role and responsibility)	r		.65	.55	.74
	p		.001**	.001**	.001**
Factor 2 (Patient/ Injured handling and Equipment use)	r	.65		.66	.66
	p	.001**		.001**	.001**
Factor 3 (Clinical decision making and practice)	r	.55	.66		.54
	p	.001**	.001**		.001**
Factor 4 (Patient/ Injured assessment)	r	.74	.66	.54	
	p	.001**	.001**	.001**	

r: Pearson Correlation Test

**p<.01

Table 6. The relationship between EMT-PCPS and Self-Efficacy-Competence Scale (n=356)

Emergency Medical Technician Professional Competence Perception Scale						
		Factor 1	Factor 2	Factor 3	Factor 4	Total Score
Self-Efficacy-Competence Scale **Total Score**	r	.28	.27	.14	.26	.27
	p	.001**	.001**	.001**	.001**	.001**

r: Pearson Correlation Test

**p<.01

Table 7. Distribution of EMT-PCPS internal consistency values (n=356)

EMT-PCPS	Number of Items	Cronbach Alpha
Professional Role and Responsibility	21	.95
Patient/Injured Handling and Equipment Use	16	.96
Clinical Decision Making and Practice	18	.94
Patient/Injured Assessment	10	.92
Total	65	.97

Table 8. Intra-class correlation coefficients between EMT-PCPS test-retest scores and their significance (n=62)

EMT-PCPS	Test Mean±SD	Retest Mean±SD	ICC	%95CI	p
Professional Role and Responsibility	6.21±0.58	6.09±0.71	.60	.41-.74	.001**
Patient/Injured Handling and Equipment Use	6.08±0.92	6.21±0.79	.67	.51-.79	.001**
Clinical Decision Making and Practice	5.61±0.90	5.79±0.85	.54	.34-.69	.001**
Patient/Injured Assessment	6.50±0.63	6.25±0.71	.63	.45-.76	.001**
Total Score	6.10±0.63	6.08±0.67	.75	.62-.84	.001**

EMT-PCPS: Emergency Medical Technician Professional Competence Perception Scale.

ICC: Interclass Coefficient Correlation

**p<.01

Discussion

The purpose of this study was to create a measurement instrument to assess the professional competence perception levels of Emergency Medical Technicians. Validity and reliability analyses were carried out for this objective. As a result of EFA conducted to reveal the factor structure within the scope of the validity studies of the scale, EMT-PCPS showed a 4-factor structure ("Professional Role and Responsibility", "Patient/ Injured Transport and Equipment Use", "Clinical Decision Making and Practice" and " Patient/Injured Assessment") and was found to explain 70.45% of the total variance. The factor loadings of the items range from .46 to .79. the explaining more than 50% of the total variation of the measuring instrument is an important criterion (27). However, item loadings greater than .30 are advised as another criterion to be taken into consideration for validity (28). The results of EFA demonstrate that EMT-PCPS fits these requirements.

The verification of the factor structure of the EMT-PCPS indicated by EFA on the data set was tested with CFA. The factor loadings acquired as a consequence of CFA can be considered to represent substantial effect sizes. The research fit criteria are among the fit indices used to evaluate model fit in Structural Equation Model (SEM) research (29). The data set appears to have a decent and acceptable fit to the model based on the reported fit criteria (30,31). The four-factor structure of the EMT-PCPS was validated based on CFA findings and specified fit criteria. The values associated with the correlation coefficients of the four factors corroborate the conclusion obtained for the factor structure of the scale items. Furthermore, item analysis findings based on upper-lower group averages reveal that the scale's items have a high degree of distinctiveness, and item-total test correlation findings show that each item is connected to and compatible with the complete scale.

The association between EMT-PCPS and the Self-Efficacy-Competence Scale was examined in the study within the context of criterion validity. According to Bandura (1986), self-efficacy belief is the process by which a person organizes and exhibits the behaviors required to execute a job or activity. The most important source of information utilized in the evaluation process is evaluations of performance success. As a result, it is hypothesized that there would be a link between professional competence perception and self-efficacy. According to these theoretical foundations, it has been determined that the two scales have a positive significant association within the context of criterion validity. The results suggest that the EMT-PCPS provides criterion validity.

When the study's reliability findings are analyzed, the EMT-PCPS Cronbach alpha reliability coefficient values range between .92 and .96 in the sub-dimensions and are .97 for the overall scale. The measuring tool's internal consistency coefficient is expected to be .70 or higher. The EMT-PCPS items can be regarded to be homogenous within themselves and capable of measuring the concept they are designed to test. Furthermore, test-retest results show that the scale is invariant over time.

The results of the validity and reliability analyses indicate that the Emergency Medical Technician Professional Competence Perception Scale can accurately measure the specified traits, without confusion with other traits, and can execute sensitive and consistent measurements across multiple assessments.

Limitations

This study was confined to final-year students in the First and Emergency Aid Program at the Vocational School of Health Services during the spring semester of the 2021-2022 academic year, and who consented to participate in the study.

Conclusion and Recommendations

Given the results of the validity and reliability findings, this measurement tool can be regarded as a valid and reliable instrument for examining the professional competence perceptions of prospective emergency medical technicians.

The "EMT-PCPS" consists of 65 items spread across the sub-dimensions of "Professional Role and Responsibility, Patient/Injured Transportation and Equipment Use, Clinical Decision Making and Practice, and Patient/ Injured Assessment". In terms of scoring, both total scores and subscale scores can be obtained for each individual, with higher scores reflecting a commendable level of professional competence perception.

EMT-PCPS will serve as an assessment tool for exploring the professional competence perceptions of final year students of the First and Emergency Aid Program. It will assist in identifying training needs to devise strategies for boosting student success and facilitating learning in the teaching process and will contribute to the development and adaptation of similar scales. In addition, it is suggested that the use of the developed scale in determining the perceptions of professional competence of emergency medical technicians

who continue the profession and emergency medical technicians who have completed all module training specified in the regulation will make significant contributions to the measurement power.

Conflict of Interest Statement

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

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All authors have made substantive contributions to the study, and all authors endorse the data and conclusions.

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ORIGINAL ARTICLE

Does Proteinuria Measured by Dipstick Method Reflect Reality in Patients with Preeclampsia?

Preeklampsi Hastalarında Dipstick Yöntemiyle Ölçülen Proteinüri Gerçeği Yansıtıyor mu?

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ABSTRACT

Aim: The aim of our study is to compare the proteinuria levels measured by dipstick in complete urine analysis at admission with the proteinuria levels measured in 24-hour collected urine for patients hospitalized with a presumptive diagnosis of preeclampsia. By doing so, we intend to review the reliability of the widely used dipstick proteinuria in patients with preeclampsia.
Material and Methods: Urine specimens were obtained from 70 pregnant women visiting high-risk maternity centers at a third-level healthcare institution. Patients were divided into four groups based on their urine dipstick screening test results: negative, +1, +2, +3, and higher. Proteinuria was considered to be present if the urinary dipstick test showed +1 or higher, while protein levels measured in the 24-hour urine collection were considered to indicate proteinuria if they exceeded 300 mg. The degree of correlation between the urine dipstick test and both 24-hour urine samples and spot urine protein-to-creatinine ratio (Pr/Cr) was compared.
Results: The mean age of the 70 preeclampsia patients in the study group was 31.7±6.2, and the mean gestational age was 32.5±4.6. The dipstick test had a sensitivity of 81.4% and a specificity of 85.2%. The dipstick test results were grouped as 0, +1, +2, +3, and higher. Statistically significant differences were detected between the groups in terms of systolic blood pressure, diastolic blood pressure, the amount of protein in the 24-hour urine, and spot urine Pr/Cr ($p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). When examining the correlation between the urine dipstick test and both 24-hour urine samples and spot urine Pr/Cr, a moderate correlation was found ($r=0.65$, $p<0.001$, $r=0.55$, $p<0.001$, respectively).
Conclusion: In hypertensive pregnant individuals, urine dipstick tests demonstrated inadequate performance in ruling out preeclampsia. Consequently, according to our investigation, we posit that the dipstick urine test can be employed as a routine and reliable diagnostic tool for preeclampsia due to its rapid results and cost-effectiveness.

Keywords: Diagnostic test accuracy, dipstick, preeclampsia, proteinuria, sensitivity, specificity.

ÖZ

Amaç: Çalışmamızın amacı, preklampsi ön tanısıyla hastaneye yatırılan hastaların kabulde tam idrar analizi ile dipstick yöntemiyle ölçülen proteinüri seviyelerini, 24 saat toplanan idrarda ölçülen proteinüri seviyeleriyle karşılaştırmaktır. Bunu yaparak, preklampsili hastalarda yaygın olarak kullanılan dipstick proteinürisinin güvenilirliğini değerlendirmeyi amaçlamaktayız.
Materyal ve Metod: Üçüncü basamak sağlık kuruluşundaki yüksek riskli gebelik merkezlerini ziyaret eden 70 gebe kadından idrar örnekleri alındı. Hastalar, idrar dipstick tarama testi sonuçlarına göre dört gruba ayrıldı: negatif, +1, +2, +3 ve daha yüksek. İdrar dipstick testi +1 veya daha yüksek gösterdiğinde proteinüri var kabul edildi, 24 saatlik idrar toplama ile ölçülen protein seviyeleri ise 300 mg'ı aştığında proteinüriyi gösterdiği kabul edildi. İdrar dipstick testi ile hem 24 saatlik idrar örnekleri hem de anlık idrar protein/kreatinin oranı (Pr/Cr) arasındaki korelasyon derecesi karşılaştırıldı.
Bulgular: Çalışma grubundaki 70 preklampsi hastasının ortalama yaşı 31.7±6.2, ortalama gebelik yaşı ise 32.5±4.6 idi. Dipstick testinin %81.4 duyarlılık ve %85.2 özgüllük gösterdiği bulundu. Dipstick test sonuçları 0, +1, +2, +3 ve daha yüksek olarak gruplandırıldı. Sistolik kan basıncı, diyastolik kan basıncı, 24 saatlik idrarda protein miktarı ve anlık idrar Pr/Cr açısından gruplar arasında istatistiksel olarak anlamlı farklar tespit edildi (sırasıyla $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$). İdrar dipstick testi ile hem 24 saatlik idrar örnekleri hem de anlık idrar Pr/Cr arasındaki korelasyon incelendiğinde, orta derecede bir korelasyon saptandı (sırasıyla $r=0.65$, $p<0.001$, $r=0.55$, $p<0.001$).
Sonuç: Hipertansif gebelerde, idrar dipstick testlerinin preklampsiyi dışlama performansı yetersiz bulunmuştur. Sonuç olarak, araştırmamıza göre, hızlı sonuçları ve maliyet etkinliği nedeniyle idrar dipstick testinin preklampsi için rutin ve güvenilir bir tanı aracı olarak kullanılabileceğini öne sürmekteyiz.

Anahtar Kelimeler: Duyarlılık, dipstick, preeklampsi, proteinüri, tanı testi, özgüllük.

Introduction

Preeclampsia is a complex pregnancy-associated condition characterized by the emergence of hypertension and proteinuria following 20 weeks of gestation, impacting around 5-8% of pregnancies globally (1). This condition poses a significant risk to both maternal and fetal health with severe cases potentially leading to maternal organ dysfunction, preterm birth, intrauterine growth restriction and increased perinatal morbidity and mortality (2). Early detection and management of preeclampsia are crucial to reduce adverse pregnancy outcomes. Proteinuria, the presence of an abnormal level of protein in the urine, is a key diagnostic criterion for preeclampsia (Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis,

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and Management Recommendations for International Practice) (3). Various methods are available for measuring proteinuria, including the gold standard, 24-hour urine protein collection, as well as spot urine protein-to-creatinine ratio (Pr/Cr) and dipstick tests (4). The dipstick method is widely used in clinical practice due to its simplicity, rapid results, and cost-effectiveness (5).

However, the accuracy and reliability of the dipstick method in measuring proteinuria among patients with preeclampsia remain controversial. Some studies have reported high sensitivity and specificity for the dipstick test (6) while others have considered it less accurate compared to the gold standard (7). No dependable approach currently exists for proteinuria screening in pregnant individuals. Due to its affordability and user-friendliness, dipstick urinalysis for proteinuria screening is the prevalent method utilized for women with low or elevated risk of preeclampsia, and this technique is endorsed by international guidelines (8, 9).

In light of these conflicting findings, our study aims to evaluate the diagnostic accuracy of the dipstick method for proteinuria measurement in patients with preeclampsia and to determine its suitability as a reliable diagnostic tool in clinical settings.

Material and Methods

Study Design

This investigation encompassed all patients diagnosed with Preeclampsia (70 pregnant individuals) admitted to the Department of Obstetrics, Health Sciences University Kütahya, Turkiye, between May 2021 and January 2023. Study participants were within the 28 to 36 weeks of gestation range and had a singleton pregnancy affected by preeclampsia, but they did not have any co-existing medical conditions. Criteria for exclusion encompassed chronic secondary or essential hypertension, autoimmune diseases like autoimmune thyroiditis, diabetes mellitus, pre-existing kidney conditions, intrauterine fetal demise, multiple pregnancies, gestational diabetes, emergency cesarean section, presence of bacteria in urine, pregnancies resulting from assisted reproductive techniques and premature membrane rupture. The study received approval from the Ethics Committee at Kutahya Health Sciences University (no: 2020/08-08) and adhered to the principles of the Declaration of Helsinki. All participants submitted written informed consent for their involvement in the study.

Patients

Following clinical and laboratory assessments in accordance with the ISSHP classification, patients diagnosed with preeclampsia were categorized into four groups based on their urine dipstick test results: 0, +1, +2, and +3 or higher. The study flow diagram can be found in Figure 1, while the baseline characteristics of the study population are detailed in Table 1.

Preeclampsia (PE) was diagnosed in patients exhibiting increased blood pressure (based on 24-hour respiratory rate records) and the recent onset of proteinuria, specifically when resting blood pressure was ≥140/90 mmHg on two separate occasions at least 4 hours apart, and significant proteinuria was detected in urine samples. If proteinuria was not present, preeclampsia was identified in women with hypertension accompanied by thrombocytopenia (platelet count <150,000/μL), impaired liver function (doubling of typical liver aminotransferase blood levels), newly developed renal insufficiency (serum creatinine levels >1.02 mg/dL), pulmonary edema, recent cerebral or visual disruptions, or uteroplacental dysfunction, such as fetal growth restriction (FGR). FGR was ascertained by a fetal abdominal circumference/estimated fetal weight <10th percentile coupled with a pulsatility index in the umbilical artery >95th percentile, a pulsatility index in the uterine artery >95th percentile, an abdominal circumference/estimated fetal weight <3rd percentile, or a lack of end-diastolic flow in the umbilical artery (10).

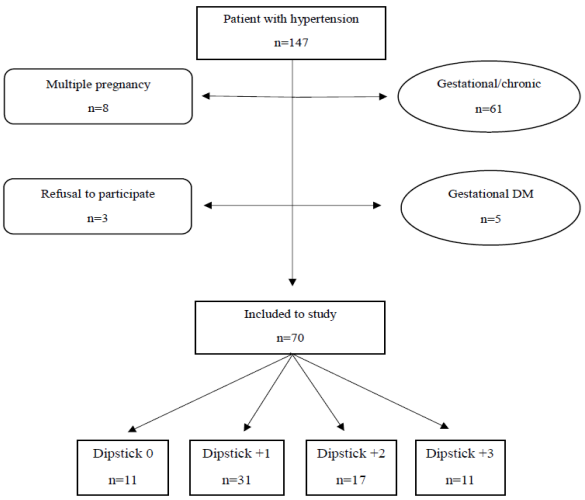

Figure 1. Study flow diagram. Patients were classified into four groups based on urine dipstick proteinuria assessment: Dipstcik non-proteinuria, +1, +2 and +3 proteinuria.

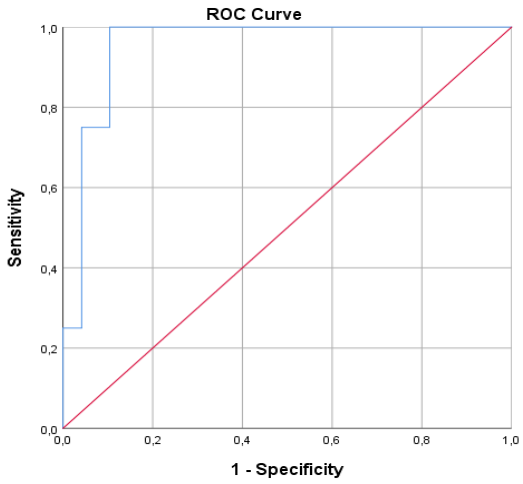

Figure 2. Correlation between the urine dipstick test and 24-hour urine protein

Table 1. Demographic and laboratory findings of the study group

	Study Group n=70
Age (year)	31.7±6.2
	32.0 [27.0; 37.0]
Parity	1.0±1.1
	1.0 [0.0; 2.0]
Gestational Age (week)	32.5±4.6
	34.0 [30.0; 36.0]
Systolic BP (mm/Hg)	146.6±15.8
	140.0 [140.0; 150.0]
Diastolic BP (mm/Hg)	89.6±10.6
	90.0 [80.0; 100.0]
Birth Weight (gr)	2670.8±660.1
	2800.0 [2320.0; 3100.0]
24h Urine Volume (mL)	2657.8±1088.2
	2550.0 [1835.0; 3475.0]
24h Urine Protein (mg)	670.0±760.2
	392.1 [178.5; 874.5]
Urine Dipstick	1.1±1.1
	1.0 [0.0; 2.0]
Urine Dansity	1030.6±119.5
	1016.0 [1008.0; 1022.0]
Urine Spot Cr (mg/dL)	77.4±38.5
	80.0 [50.0; 95.0]
Urine Spot Protein (mg)	40.3±66.5
	21.0 [8.0; 38.0]
Spot Urine Pr/Cr	0.5±0.6
	0.3 [0.2; 0.6]
Albumin (gr/dL)	3.0±0.4
	3.0 [2.8; 3.3]
Thrombocyte (10^3/µL)	218.4±63.3
	221.5 [166.0; 257.0]
AST (U/L)	76.2±278.4
	21.0 [16.0; 37.0]
ALT (U/L)	44.7±130.0
	13.0 [9.0; 19.0]
Direct Bil (mg/dL)	0.1±0.1
	0.1 [0.1; 0.1]
Ind Bil (mg/dL)	0.4±0.2
	0.3 [0.2; 0.5]

Values are presented as mean±SD, median [interquartile range], n; number, Abbreviations BP; Blood pressure, h; hours, Cr; Creatinin, Pr; Protein, AST; aspartate aminotransferase, ALT; alanine transaminase, Bil; Billirubi, Ind; Indirect.

Methods

Proteinuria evaluation involved the use of urine dipstick tests, spot urine Pr/Cr, and total protein measurements in 24-hour urine samples for each patient during their hospital stay. The urine dipstick test was conducted twice, with a positive result deemed significant. Following this, creatinine, AST, ALT, and complete blood count (CBC) were assessed. Serum and urine biochemical parameters were analyzed using the Architect analytical system (Abbott) while CBC was analyzed with the Sysmex analytical system (Sysmex). The urine dipstick test was carried out using the Iris urinalysis system (Beckman Coulter).

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was employed to assess normal distribution. For multiple comparisons of normally distributed data based on group, a one-way analysis was utilized, and the Tukey HSD test was applied for paired comparisons. The Kruskal Wallis test was used for multiple comparisons of non-normally distributed data according to group, and Bonferroni correction employed for paired comparisons. Quantitative data analysis results were reported as mean ± standard deviation and median [interquartile range] while categorical data were presented as frequency (percentage). A p-value below 0.05 was deemed statistically significant in all tests.

Results

During the period from May 2021 to January 2023, a total of 70 women were diagnosed with pre-eclampsia. Among them, 59 had proteinuric disease and 11 had non-proteinuric disease. Demographic and laboratory features of these 70 preeclamptic women are detailed in Table 1. The urine dipstick test was conducted on preeclamptic pregnant women to determine proteinuria levels. The results showed that 11 were non-proteinuric, 31 had +1 proteinuria, 17 had +2 proteinuria, and 11 had +3 proteinuria. The grouping of preeclamptic pregnant women based on urine dipstick results and their comparison with other proteinuria measurement methods are presented in Table 2.

Table 2. Comparison of Other Variables According to Urine Dipstick Protein Measurement

	Dipstick 0 n=11	Dipstick +1 n=31	Dipstick +2 n=17	Dipstick +3 n=11	p value
Systolic BP (mm/Hg)	142.6±10.9	144.5±6.9	144,1±9,4	163,6±28,0	0.001[a]
	140.0 [140.0; 150.0]	140.0 [140.0; 150.0]	140,0 [140,0; 150,0]	160,0 [140,0; 180,0]	
Diastolic BP (mm/Hg)	85.5±8.9	87,3±6,5	89,4±8,3	103,6±10,3	<0.001[b]
	80.0 [80.0; 90,0]	90,0 [80,0; 90,0]	90,0 [90,0; 90,0]	100,0 [100,0; 110,0]	
24h Urine Protein (mg)	262,3±189,6	683,3±667,0	900,4±612,6	2276,4±1252,2	<0.001[a]
	213,8 [133,7; 321,0]	439,5 [182,4; 874,0]	852,1 [456,0; 1015,0]	1831,3 [1572,8; 2980,0]	
Spot Urine Pr/Cr	0,2±0,3	0,6±0,6	0,5±0,5	1,4±0,7	<0.001[a]
	0,2 [0,1; 0,3]	0,4 [0,2; 0,8]	0,4 [0,2; 0,5]	1,1 [0,8; 2,2]	

Values are presented as mean±SD, median [interquartile range], Abbreviations; BP:Blood pressure, h:hours, Pr:protein, Cr:creatinin n; number. p-values were calculated with [a]One-way ANOVA or [b]Kruskal Wallis test. The significant pairwise group comparison results were as represented below; For systolic BP: 0 vs 3: p<0.0001, 1 vs 3: p=0.013, 2 vs 3: p=0.004, (Post Hoc test: Bonferroni), For Diastolic BP: 0 vs 3: p<0.001, 1 vs 3: p<0.001, 2 vs 3: p<0.001 (Post Hoc test: Tamhane's T2) For 24h Urine Protein: 0 vs 2: p=0.006, 0 vs 3: p<0.001, 1 vs 3: p<0.001, 2 vs 3: p<0.001 (Post Hoc test: Bonferroni), For Spot Urine Pr/Cr: 0 vs 3: p<0.001, 1 vs 3: p=0.009, 2 vs 3: p=0.001.

Proteinuria was evaluated using three different methods, namely urine dipstick test, spot urine Pr/Cr, and total protein in a 24-hour urine sample. In the preeclamptic group, 10% (7/70) of the patients had a falsely negative result on the urine dipstick test while 6% (4/70) had a false positive result. When compared to proteinuria in the 24-hour urine, the urine dipstick test had a sensitivity of 81% and a specificity of 85%. The correlation between the urine dipstick test values and 24h urine protein values is shown in Figure 2. There was a significant relationship between the urine dipstick test and the 24h urine protein, with a correlation rate of r=0.65, p<0.001. The area under the ROC curve (AUC) (Fig. 2) was 0.95. There was a significant relationship between the spot urine protein/creatinine and the 24h urine protein, with a correlation rate of r=0.77, p<0.001. When compared to proteinuria in the 24-hour urine, the spot urine Pr/Cr had a sensitivity of 88.4% and a specificity of 88.9%.

Preeclamptic patients were divided into 4 groups as urine dipstick test result 0,+1,+2,+3 and above. The groups were compared between themselves with the results of systolic BP, diastolic BP, 24h urine protein and spot urine Pr/Cr.

In the urine dipstick test groups, there is a statistically significant difference between the systolic blood pressure (BP) values (p=0.001). Upon conducting a subgroup analysis for systolic BP values, a statistically significant difference was observed between the dipstick test results of 0 and +3, +1 and +3, and +2 and +3 and above groups (p<0.001, 0.013, and 0.004, respectively). Furthermore, a statistically significant difference was found between diastolic BP values in the urine dipstick test groups (p<0.001). When performing a subgroup analysis for diastolic BP values, a statistically significant difference was noted between the dipstick test results of 0 and +3, +1 and +3, and +2 and +3 and above groups (p<0.001 for all three comparisons).

There is also statistically significant difference between the 24-hour urine protein values in the urine dipstick test groups (p<0.001). Upon examining the subgroup analysis for 24-hour urine protein values, there was statistically significant difference between the dipstick test results of 0 and +2, 0 and +3, +1 and +3, and +2 and +3 groups (p=0.006, <0.001, <0.001, and <0.001, respectively). Lastly, a statistically significant difference was observed between the spot urine Pr/Cr ratios in the urine dipstick test groups (p<0.001). When analyzing the subgroup analysis for spot urine Pr/Cr ratios, there was statistically significant difference between the dipstick test results of 0 and +3, +1 and +3, and +2 and +3 groups (p<0.001, 0.009, and 0.001, respectively).

Discussion

The primary objective of this study was to assess the reliability of the urine dipstick test in confirming significant proteinuria in pre-eclampsia as a diagnostic tool. Moreover, the study aimed to establish an optimal threshold for diagnosis confirmation. The results of this investigation indicate that the urine dipstick test can be an effective diagnostic tool for pre-eclampsia as it demonstrated a moderate correlation (r=0.65, p<0.001) with 24-hour urine protein and had an AUC of 0.95.

The dipstick analysis, which employs reagent strips for visual examination, offers a rapid, convenient and straightforward method. Nonetheless, urine samples are collected at different times throughout the day. This test presents challenges due to its relatively high rates of false positives and false negatives (6, 11, 12). As a result, it is typically succeeded by the gold standard test, the 24-hour urine collection, for verification. In the studied group, spot urine Pr/Cr ratio and urine dipstick test were both determined to be suitable for diagnosing preeclampsia. Their sensitivity and specificity levels were sufficiently high for accurately identifying preeclampsia patients. However, although the 24-hour urine test is deemed the gold standard for proteinuria assessment, the test is intricate, labor-intensive, and susceptible to pre-analytical errors (13). These factors may lead to patient noncompliance and discomfort. As demonstrated earlier, the spot urine Pr/Cr remains unaffected by fluctuations in urine concentration and the volume of urine excreted over a 24-hour period (14). Our research reveals that spot urine Pr/Cr is as useful as the 24-hour urine test for patients with preeclampsia. Moreover, a spot urine Pr/Cr threshold of 0.3 mg/dL aligns with proteinuria observed in the corresponding 24-hour urine sample.

In a meta-analysis comprising 19 studies by Teeuw et al., it has been demonstrated that, in pregnant women with suspicion of preeclampsia at or beyond the 20th gestational week, automated measurements of urine dipstick tests were more sensitive compared to manual assessments. They also discovered that the sensitivity of spot urine Pr/Cr measurements was similar to that of urine dipstick tests (15). In the January 2020 publication of the American College of Obstetricians and Gynecologists (ACOG) guideline titled "Gestational Hypertension and Preeclampsia," it has been shown that urine dipstick tests with +1 proteinuria yield false-positive results in 71% of cases, while +3 proteinuria leads to a 7% false-positive rate. The guideline suggests that adopting a threshold of +2 proteinuria for the diagnosis of proteinuria in preeclampsia, when compared to 24-hour urine collection results, would provide a more accurate assessment (16, 17). In our study, among 31 preeclamptic pregnant women with +1 proteinuria on urine dipstick tests, 4 were false-positive cases (13%). In a study examining the diagnostic performance of urine dipstick tests for the prediction of significant proteinuria in pregnancy, 2212 urine samples from 1033 women were analyzed. The false-positive rate for 1+ on the dipstick test was notably high at 78% (18). In our study involving 70 preeclamptic pregnant women, the false-positive rate for preeclamptic patients with a +1 urine dipstick test result, based on the 24-hour urine proteinuria findings, was found lower compared to the rates reported in the literature. Stefanska et al. found similar results to our study with 88 patients. In their investigation comparing two groups with preeclampsia and gestational hypertension, they discovered

that 9% (4/44) of the urine dipstick results were false positive in the preeclampsia group, consisting of 44 pregnant women (19). There are several factors that could contribute to the observed differences in false-positive rates between our study and the literature. First, variations in patient demographics, clinical characteristics and disease severity among the study populations may lead to different outcomes. Second, the possibility of random variation in the results, as sample size and statistical power can influence the observed rates. The lower false-positive rate observed in our study may be attributed to a smaller sample size or other factors unique to our study population.

Despite the high false-positive rates reported in the literature for the urine dipstick test, there is still a need for a rapid, economical, highly sensitive and specific test to detect the presence of proteinuria in pregnant women with suspected preeclampsia during the referral process (20). Although the 24-hour urine collection is the gold standard for diagnosing proteinuria, waiting for 24 hours in pregnant women with suspected preeclampsia can lead to delayed diagnosis. Therefore, in the past decade, the use of the spot urine Pr/Cr test has been increasingly adopted in clinics for rapid proteinuria diagnosis (21). In recent years, several studies have compared the efficacy of the spot urine Pr/Cr and the 24-hour urine test in diagnosing preeclampsia in pregnant women. In a meta-analysis by Geneen et al., which included 29 studies, a spot urine Pr/Cr threshold of 0.3 mg/dL demonstrated high diagnostic accuracy in identifying significant proteinuria when compared to the reference test of a 24-hour urine collection, with a sensitivity of 91% and specificity of 89% (22). In the same study, it was discovered that when using a PCR threshold above 60 mg/mmol, specificity remained consistently high (albeit with lower sensitivity), allowing for the identification of clinically significant proteinuria with a positive test result. Conversely, at a threshold below 30 mg/mmol, sensitivity was consistently high (despite lower specificity), enabling the exclusion of clinically significant proteinuria with a negative test result. The variability in results between 30 and 60 mg/mmol indicates a grey area, suggesting the potential necessity for repeated PCR testing within this range.

Limitation of our study is the small sample size consisting of a limited number of patients. Among the strengths of our research is the inclusion of only patients diagnosed with preeclampsia according to the ACOG criteria, and another strength is the separate evaluation and comparison of urine dipstick protein levels.

Conclusion

In conclusion; a key finding of our study is the significant correlation between the urine dipstick test, spot urine Pr/Cr and proteinuria in 24-hour urine samples. Although the latter serves as the gold standard for diagnosing proteinuria, it postpones the diagnosis by 24 hours, it is poorly tolerated by patients, and is unsuitable for emergency room settings. Timely decision-making can potentially alleviate patients' anxiety, decrease hospital stays, reduce associated costs, and facilitate the treatment of women with genuine pathological conditions.

Disclosure of interests

The authors declare that they have no conflict of interest.

Contribution to Authorship

CS and MMI conceived and designed the study; CS, performed the experiments, contributed reagents, materials and analysis tools, MMI analyzed the data, CS and MMI drafted the manuscript. CS participated in the writing of the final version of the manuscript.

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ORIGINAL ARTICLE

Women's Perception of Sexuality and Sexual Violence in Turkish Culture - Are Women Aware of This Difficult Distinction? : A Qualitative Research

Türk Kültüründe Kadınların Cinsellik ve Cinsel Şiddet Algısı - Kadınlar Bu Zor Ayrımın Farkında Mı?: Niteliksel Araştırma

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ABSTRACT

Background/Aims: In this study, we aimed to determine the perceptions of women of reproductive age with active sexual lives living in the northwest of Turkiye, and whether they are aware of sexual desire and sexual violence they encounter in their sexual lives.
Methods: This qualitative study was carried out with 18 women by in-depth interviews. In-depth and semi-structured interviews were conducted between December 2021- July 2022. Content analysis was used for data analysis.
Results: Three themes were identified in the study: (1) the building block of marriage (2) sexuality as violence (3) the effects of sexual violence. The participants emphasized that their different expressions of sexuality from their groups. When they do not feel sexual desire, the sexual function is an act of violence in which the woman is the object of sex. Sexual harassment, some women were also exposed to verbal and psychological violence of a sexual nature.
Conclusion: At the end of the research, it was determined that women often perceived sexuality as a fundamental element for the continuation of marriage and commitment to their spouses. Participants stated that they were sometimes exposed to sexual violence and different types of violence in their sexual lives.

Keywords: Perception, sexuality, sexual violence, violence, women

ÖZ

Amaç: Bu çalışmada Türkiye'nin kuzeybatısında yaşayan aktif cinsel hayatı olan üreme çağındaki kadınların, cinsel hayatlarında karşılaştıkları cinsel arzu ve cinsel şiddetin farkında olup olmadıklarına dair algılarını belirlemeyi amaçladık.
Gereç ve Yöntem: Bu nitel çalışma, 18 kadınla derinlemesine görüşme yapılarak gerçekleştirilmiştir. Aralık 2021-Temmuz 2022 tarihleri arasında derinlemesine ve yarı yapılandırılmış görüşmeler gerçekleştirilmiştir. Verilerin analizinde içerik analizi kullanılmıştır.
Bulgular: Çalışmada üç tema belirlendi: (1) evliliğin yapı taşı (2) şiddet olarak cinsellik (3) cinsel şiddetin etkileri. Katılımcılar cinselliği evliliğin ve eş sadakatinin devamı için temel bir unsur olarak görmekteydi. Katılımcılar cinselliği erkeklerin farklı düşündüklerini, cinsel istek olmadığında cinsel işlevin kadının seks objesi olduğu bir şiddet eylemi olduğunu vurguladı. Cinsel şiddetin yanı sıra bazı kadınlar cinsel içerikli sözel ve psikolojik şiddete de maruz kalmaktaydı.
Sonuç: Araştırmanın sonunda kadınların cinselliği sıklıkla evliliğin devamı ve eşlerine bağlılığın devamı için temel bir unsur olarak algıladıkları belirlendi. Katılımcılar zaman zaman cinsel yaşamlarında, cinsel şiddete ve şiddetin farklı türlerine maruz kaldıklarını belirtti.

Anahtar Kelimeler: Algı, cinsellik, cinsel şiddet, şiddet, kadın

Introduction

Sexuality includes how people perceive their sexual identity, consider themselves or others as a sexual entity, have knowledge and experiences of sexuality through biological, social and cultural environmental factors, and discover physical and spiritual desire and pleasure alone or with others (1). Each individual's willingness to participate in sexual acts whenever and wherever they want protects and strengthens their biopsychosocial health, reduces sexual dysfunctions and prevents exposure to sexual life-based violence (2).

The World Health Organization (WHO) stated that sexual violence is against the fields of Good Health and Well-Being, Gender Equality and Peace Justice and Strong Institutes of the Global Goals for Sustainable Development that should be achieved by 2030 (3). Sexual violence affects people of all ages, genders and sexual orientations and causes serious negativities at the social level. Perpetrators of sexual violence are often the victim's current or former partner, acquaintance, neighbor or family member (4). Violence against

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women affects not only the targeted women, but also family members and society, and can cause serious health problems. The physical and mental health of women deteriorates, their self-confidence decreases, and they cannot get out of the situation by behaving submissively. For this reason, it is important to know that violence against women is an important problem that should be prevented (5).

Although sexual violence is very common among women globally, it is emphasized that 1 in 3 women experience sexual violence and harassment (4). The results of studies on domestic violence experienced by married women in Turkiye are comparable with world data (6). According to the 2012 "Women's Empowerment and Gender Equality" report published by the United Nations; 22.0% of women living in Denmark, 25.0% of women in Germany, 13.9% of those living in Norway have experienced physical and/ or sexual violence at any point in their lives by their spouse or partner or one of them (7). According to official statistics in Turkiye, 44% of domestic violence is emotional, 36% is physical, 38% is both physical and sexual, 30% is economic and 12% is sexual violence (8).

Sexual Violence

Sexual violence is an important human rights violation that includes both sexual harassment and assault, producing negative consequences for physical and mental health (9). Sexual violence is not a reflection of sexual desire, it is an aggressive act mostly perpetrated by men against women, reflecting feelings of anger and hostility as well as the need to exert power and control (10). Sexual violence refers to any sexual experience that jeopardizes freely given sexual consent. Sexual violence can include forced sexual intercourse (rape), sexual coercion (unwanted verbal or psychological pressure designed to promote sexual compliance), and voluntary sexual compliance (willingness to consent to unwanted sex despite the absence of sexual desire) (11).

Victims of sexual violence may be unaware that their sexual rights have been violated. Therefore, they are unlikely to report sexual violence or leave their sexually challenging relationship. Because male and female sexuality are positioned very differently in societies with pronounced gender roles and gender inequality, the probability of sexual violence in marriages is higher in such societies (12). In cultures with intense gender inequality, women are assigned to meet the sexual needs of their husbands (13). Indeed, a normative and gender-based (traditional) heterosexuality including men presumed to need sex and sexually passive and sensitive women creates a sociocultural framework for sexual violence (14). Insufficient education and economic resources of women, their desire to be an "obedient and good wife" accepted by their husbands and society, their perceived responsibility for meeting the needs of their husbands and protecting their marriage form a basis of an unwanted sexual relationship, namely sexual violence (15).

The Current Study

When the studies conducted on a provincial basis in Turkiye to determine the prevalence of sexual violence are examined, it is seen that women are frequently exposed to sexual violence by their husbands or partners at 4.0% (16), 4.9% (5) levels that should not be underestimated. In a study conducted across Turkiye, 12% of all married women stated that they were exposed to sexual violence at some point in their lives. There are also differences between regions of Turkiye in the incidence of sexual violence. The northeastern region of Turkiye has the highest rate of sexual violence with 16% (17). In the light of this information, it was thought that women might not be able to distinguish between sexual intercourse that develops freely within the framework of sexual desire and desire in heterosexual relationships, and the sexual act, that is, the experience of sexual violence, which must be obligatory participation. Sexuality is a lifelong necessity. Sexual violence is a problem that can be encountered in all periods of life. However, a decrease in the quality of sexual life can be observed during adolescence, when a woman's body and genital organs have not completed their development sufficiently, and during menopause and old age, which are characterized by a decrease in hormone levels. The period in which women maintain quality sexual function in terms of anatomical, hormonal and psychosocial aspects can be considered as the reproductive age (8,9,15). In this respect, in this study, we aimed to determine the perceptions of women of reproductive age with active sexual lives living in the northwest of Turkiye, and whether they are aware of sexual desire and sexual violence they encounter in their sexual lives.

Materials and Methods

Study Design and Participants

The study has adopted an exploratory qualitative research design to obtain a profound understanding of the women's perceptions and experiences of sexual violence risk. The sample included a total of 18 participants. The study employed a convenient sampling technique due to the limited number of available, accessible, and eligible candidates to be included in this study. Participants were not required to be married or not. Apart from this, inclusion criteria include: (1) Having an active sexual life (2) Being in the reproductive age (18-49 years) (3) Having no history of chronic disease (4) Not being diagnosed with breast or gynecological cancer (5) Agreeing to participate in the study. We determined the number of required respondents by interviewing patients who met the inclusion criteria until the data were saturated, and no new topics were generated. Table 1 shows the participants' characteristics.

Data Collection

This qualitative study was conducted with a total of 18 women by in-depth interviews. Individual, in-depth and semi-structured interviews were held between December 2021 and July 2022 to protect women's

privacy. The two authors (ECE, AK) contacted participants prior to interviews to ascertain if there were any changes in their condition. Participants were informed about the identity of the researchers. They were also informed about the study (its purpose, the confidentiality of the responses, where and how the data would be kept). Participation was on a volunteer basis. Participants were asked for their consent to have the discussions recorded on a voice recorder. Each interview took around 30-45 minutes.

The data were collected using a "semi-structured interview form" that was prepared by the researchers based on the literature (11,14). The interview form contained open-ended questions regarding the participants' perceptions of sexuality and sexual violence risk. The questions in this form were as follows:

(1) What is the place and significance of sexual intercourse in marriage?

(2) What are the factors affecting sexual intercourse?

(3) What is sexual violence?

(4) How women who are exposed to sexual violence in their marriage are affected?

A semi-structured interview form was prepared by the researchers. Then, expert opinions were obtained from five faculty members who are experts in their fields. It is important to ensure data saturation in qualitative research. In qualitative interviews, data saturation is reached when the researcher begins to hear the same comments over and over again (18,19). Accordingly, the number of participants to be included in the sample varies in order to ensure data saturation. In this study, the researchers ended the interviews by repeating the same data.

Ethical Approval

The protocol for the research has been approved by the Bartin University Social and Human Sciences Ethics Board (Date: 16.12.2021, Approval Number: 2021-SBB-0487). Institutional permission to carry out the research was obtained from the Bartin Provincial Health Directorate (Approval Number: E26080346-799). The participants were informed about the study, and their verbal and written consent was obtained. The research complies with the provisions of the Declaration of Helsinki (as revised in Brazil 2013).

Data Analysis

It is very important to pay attention to meticulousness in qualitative research. Rigor in qualitative research; It makes the data collection and analysis process systematic, orderly and traceable. In this research, great attention was paid to meticulousness. The data of the study were collected from all participants by the same researcher. The questions stated in the research questions were not deviated, and the same questions were asked to each participant in the same way. We analyzed transcripts using the thematic approach of Braun and Clarke (2006) (18). In line with this approach, data analysis was carried out in six steps. Beforehand, the audio recordings obtained from the interviews were converted into written documents by two researchers. In the first step, researchers became familiar with the data through rereading and note-taking. In the second step, systematic codes for the data were created. The researchers created a series of code lists (19). In the third step, possible themes were formed by examining the first codes and data obtained in detail. In the fourth step, the themes were created and the codes placed in the themes were reviewed to ensure that the data were suitable for the research questions. In the fifth step, the names, scopes and definitions of the themes were prepared. The final step was the reporting of the findings. The analysis of the research data was carried out independently by two researchers, and then the researchers decided on the themes and sub-themes together. The participants were contacted to avoid doubts during data confirmation. In addition, feedback on the precision and reliability of the themes was received from the interviewed patients (20). This current study was presented by arranging it according to the combined criteria for reporting qualitative research (COREQ) checklist for qualitative research (21).

Results

Table 2 presents the themes that emerged as a result of the thematic analysis of the data obtained from the semi-structured interviews. Three themes were identified in the study: (1) the building block of marriage (2) sexuality as violence (3) the effects of sexual violence. The first theme, sexuality as the building block of marriage, had four sub-themes. These were; necessity, perception difference between men and women, duty and conditions of sexuality.

The second theme was sex as violence and had three sub-themes. These were; It was sexual object, abuse and verbal sexual violence. The final theme was effects of sexual violence. It had three sub-themes; physical effects, psychological effects and effects on marriage.

Theme 1: Building block of marriage

On the theme of the building block of marriage, women stated that sexuality/sexual intercourse is necessary for marriage, that men and women look at sexuality from different perspectives, that sexuality should not be seen as a duty in marriage, and that there are conditions for a healthy sexual relationship.

Seven of the participants have emphasized the necessity of sexuality/sexual intercourse for marriage. Some of their statements were as follows:

"Sex is an important part of marriage. Sexuality is also a factor that pushes individuals to marry. Because sexuality is an act that is accepted in our society by marriage." Participant 8

"If there is no harmonious sexual life between the spouses, this may be a reason for divorce. It is important for spouses to have sexual compatibility, dyadic adjustment, and understanding each other.

Therefore, marital harmony is also very necessary for marriage." Participant 2

Eight of the participants have stated that men and women have different points of view on sexuality, and therefore they have different expectations from sexuality in marriage:

"I think sex is a chore. It is not necessary for me. However, it is a must-have for men and something that exists to make them happy." Participant 11

"Sex is necessary for men to build trust and loyalty in marriage. The important thing for me is to have a pleasant time with him, to be able to understand him, to share good moments with him. But they do not consider like that. According to men, sexual intercourse is a must for the continuation of marriage." Participant 12

Some women stated that they saw sexuality as an obligation and a duty in their marriages. Some of the participants' statements on this subject were as follows:

"If a woman is subjected to sexual violence by her husband, she feels inadequate, she only fulfills the tasks assigned to her in marriage due to the fear of losing her husband." Participant 9

"There are times when I do not want to have sexual intercourse, I mean when I am tired, I need rest, and I feel bad psychologically. I am not a robot. But according to my husband, when he wants to have sexual intercourse, I should also want it too and I have to be ready immediately (for sexual intercourse)." Participant 12

Almost all of the participants have several conditions for a healthy sexual relationship, including sexual desire/adjustment, personal boundaries, and emotional attachment.

"Sexuality consists of desire, willingness, passion, and intense pleasure. The reluctance of even one of the couples in sexual intercourse affects their relationship negatively after a while. That is why desire is important in sexual intercourse." Participant 1

"We need to be able to do this (sexual intercourse) within the limits of mutual trust between spouses, and most importantly, we need to know the limit of the other, we need to know how far we can go." Participant 4

"Emotional bond is the most important thing in a sexual relationship. If there is an emotional bond between the spouses, I do not think such a situation (sexual violence) will occur." Participant 9

"Desire is important in sex life. If one of the spouses is not willing to have sexual intercourse, this will also affect the other, therefore the marriage may break down, they may begin fighting, their trust in each other is shaken, and the marriage may even end." Participant 7

Theme 2: Sexuality as violence

On the theme of sexuality as violence, women stated that they were seen as sexual objects by their husbands, that sexual violence was abuse, and that they could also be subjected to verbal sexual violence.

Some of the participants described it as sexual violence when men considered women sexual objects. Their statements were as follows:

"Sexual violence refers to a man's insistently forcing his wife when she does not want to have sex, considering her as "an always ready-to-use machine" and starting sexual intercourse directly without a nice word or small gesture." Participant 7

"Since I work in a night shift job, when I go home in the morning, my husband wants to have direct sexual intercourse without preparing a breakfast for me, without a nice word or a smiling face, it really makes me angry. I am not a sex object or a sex machine." Participant 9

Almost half of the participants have stated that sexual violence is a type of abuse, even if it occurs among married people. Their statements on this subject were as follows:

"Sex is pleasurable when it is optional. Here, if there is no pleasure and pleasure in sexual intercourse, then it turns into rape." Participant 3

"I think the partner's endless and unlimited desires in sexual life are sexual violence. Because even if women do not want to have sex, men can have sexual intercourse due to their endless desires and abuse women just because they want sex." Participant 7

Six of the participants have stated that sexual violence can occur not only through physical contact but also verbally. Their statements were as follows:

"When I took off my clothes, I was very annoyed by his statements like "did you have a belly?", "did you gain weight?", "you are not fit as before". Unfortunately, men always consider themselves as superior and women as inferior." Participant 9

"Besides a direct touch or sexual intercourse, he may also say something that denigrates or insults my sexuality. Men's mouths get a little dirty and they can't think in detail like women." Participant 12

Theme 3: Effects of sexual violence

In the theme of the effects of sexual violence, women talked about the physical and psychological consequences of sexual violence and stated that it could cause disagreements between spouses/ partners.

Six of the participants have stated that sexual violence/forced intercourse can have some physical consequences such as bleeding in women. Their statements were as follows:

"In one of my shifts, a sex worker came to be examined because she was exposed to sexual violence from her partner. Her physical and psychological condition was so bad, she was examined and cared for, but she was still bleeding." Participant 5

"If a woman does not want to have sex, she may experience undesirable situations such as vaginal bleeding and tearing due to lack of adequate vaginal lubricity." Participant 9

Almost all of the participants have emphasized that sexual violence have negative psychological effects on women:

"The quality of life of a woman who experiences sexual violence from her husband in her marriage decreases, she cannot enjoy life, does not want to involve in society, and feels guilty. However, maybe there is no fault of the woman here." Participant 3

"If a woman is sexually abused by her husband, she looks for the cause of every event in herself, consider herself failed in her marriage, and ultimately becomes unhappy." Participant 4

More than half of the participants have stated that sexual violence can cause conflict between spouses and end their marriage.

"If a woman experiences sexual violence in her marriage, she is completely alienated from her husband, her trust in her husband is broken, and this negatively affects all marriage processes." Participant 5

Table 1. Participants' characteristics

Informant	Age	Educational level	Employment status	Duration of marriage (year)	Type of marriage
Participant 1	29	Graduate	Employed	3	Love marriage
Participant 2	38	Undergraduate	Employed	10	Love marriage
Participant 3	31	Undergraduate	Employed	6	Love marriage
Participant 4	27	Undergraduate	Employed	2	Love marriage
Participant 5	33	High school	Employed	5	Arranged marriage
Participant 6	31	Undergraduate	Employed	2	Love marriage
Participant 7	28	Undergraduate	Employed	1	Love marriage
Participant 8	32	Undergraduate	Employed	2	Love marriage
Participant 9	41	Undergraduate	Employed	19	Love marriage
Participant 10	40	Undergraduate	Employed	12	Love marriage
Participant 11	42	Undergraduate	Employed	10	Arranged marriage
Participant 12	45	Primary school	Unemployed	34	Arranged marriage
Participant 13	45	Primary school	Unemployed	0	Arranged marriage
Participant 14	38	High school	Employed	10	Arranged marriage
Participant 15	31	Undergraduate	Employed	6	Love marriage
Participant 16	27	Undergraduate	Employed	2	Love marriage
Participant 17	33	High school	Employed	5	Arranged marriage
Participant 18	44	Undergraduate	Employed	14	Arranged marriage

Table 2. Theme and sub-themes

Themes	Building block of marriage	Sex as violence	Effects of sexual violence
Sub-Themes	Necessity (n=9)	Sexual object (n=5)	Physical effects (n=6)
	Perception difference between men and women (n=8)	Abuse (n=7)	Psychological effects (n=14)
	Duty (n=5)	Verbal sexual violence (n=6)	Effects on marriage (n=9)
	Conditions of sexuality (n=12)		

Discussion

This study aimed to examine women's perceptions of sexuality and sexual violence risk using qualitative methods. The themes were: (1) building block of marriage (2) sexuality as violence (3) effects of sexual violence. Participants were aware of sexual violence when sexual intercourse took place against the will of one party, even if it was between married people. They saw this as a risk to their health. It was stated that sexual violence could be seen not only as sexual intercourse but also verbally.

The theme of "building block of marriage" is derived from the participants' expressions that reveal their feelings, thoughts and experiences related to sexuality, such as the difference between men and women, the perception of sexuality as a marriage duty, and the conditions of sexuality including sexual desire, harmony, and personal boundaries. In the present study, participants have stated that the significance of sexuality for the continuation of marriage is undeniable. Studies have reported that unlike women, men cannot control their sexual desire, and when men want to have sex, women fulfill this demand to avoid major problems such as fighting and divorce (11,14). Yang et al. (2016) have argued that women are expected to meet their husbands' sexual needs regardless of their own desires to maintain marital and family harmony (22). In a qualitative study conducted by Farvid and Saing (2022) in Cambodia, it was stated that a woman's refusal of sexual intercourse in her marriage may result in her being beaten by her husband, being separated from her children, her husband finding a mistress, or not being able to provide financial support for herself and her children (11). For these reasons, women may have sexual intercourse and fulfill their marital duties in line with the demands of their husbands, against their wishes and desires, to ensure the continuation of their marriage.

In the present study, participants have emphasized that sexual intercourse requires sexual desire, sexual harmony and protecting personal boundaries. In the study of Balarabe (2022), one third of the participants reported to have the right to discover and use their sexual preferences freely, whereby their freely given consent should be asked before sexual intercourse (9). One study has determined that men use sexual coercion as a tool for sex when women do not consent to sexual intercourse (12). Thanks to increased access to information in modern societies and spread of

sexual education compared to previous years, women in modern societies can make choices about their own sexuality, however, men in patriarchal societies are still a decision-making power over women (11). In this regard, it is thought that it is very important in the context of sexual rights for women to respect their decisions freely, without pressure or coercion in sexual life.

In our study, participants drew attention to the violence dimensions of sexuality. They have stated that men consider women as sexual objects and want to have sexual intercourse without establishing an emotional bond or saying a nice word; and even worse, women are exposed to men's sexual and physical humiliations. One of the reasons why men consider women sexual objects may stem from gender-based social messages stating that women have a role of being mothers and fulfilling their husband's sexual needs (11,23). Abdolmanafi et al. (2022) have found that some participants consider women as a means to satisfy men's sexual desire and sexual satisfaction (14). Gender roles that privilege men and normalize sexual coercion and violence against women cause women to be exposed to sexual violence, making sexual violence acceptable by social learning (12). In this regard, while transferring information to new generations, it is important to purify sexuality from violence, especially for women, along with the developments in gender roles, especially with the influence of sexual health training given.

In the present study, participants have stated that sexual violence is an abuse and can occur in both physical and verbal forms. When partners have sexual pleasure and orgasm in sexual act, there is no abuse and sexual violence. In a heterosexual sexual intercourse, if partners have a respectful, reliable and satisfactory communication, then their sexual pleasure facilitates sexual intercourse and orgasm (1). However, several studies have reported that women have less pleasant sexual experience compared to men and are exposed to many humiliating and contemptuous words, threats and behaviors during sexual acts, and therefore, their probability of experiencing a positive sexual life decrease (1,11,24). In addition, one study found that one participant did not feel any desire during sexual intercourse and was tired of having sex with her husband, but had to have sexual intercourse without being satisfied because her husband wanted it (11). It is thought that when all individuals respect sexual desire, the concept of sexual violence will disappear and the quality of sexual life will increase by providing pleasant and positive sexual experiences.

In our study, participants have stated that sexual violence and forced intercourse can have some physical consequences, such as bleeding in women. In one study, a woman with uterine prolapse stated that although she had bleeding and pain during sexual intercourse, she felt sorry for her husband because she could not have sex with him, and despite this she tried to have sex with him (11). In a different study, it is stated that the negative physical effects of sexual violence are more common in young women due to physical disabilities and mobility limitations in men, and that there are no significant differences in terms of psychological and verbal violence (24).

In this study, almost all of the participants have emphasized that sexual violence can have negative psychological effects (humiliation, stigma, feeling worthless, guilt, etc.) on women. Women are exposed to various forms of sexual violence such as staring, verbal abuse, and non-consensual touching (10). In addition, women are socially excluded and isolated in societies that blame female victims of sexual violence (25). As a result, women feel offended, humiliated and worthless (11). Since the feelings, thoughts and wishes of women are not valued in sexual violence, it creates a traumatic effect on their psychology (24). Women who have been sexually abused may hesitate to seek help for various reasons, including cultural factors (25).

In our study, more than half of the participants have stated that sexual violence can cause conflict between spouses and end their marriage. Studies indicate that some women engage in sexual intercourse to survive their marriage and meet their husbands' sexual needs (11,14). In this context, it is thought that sexuality for women is perceived as a duty that must be fulfilled for the continuation of the marriage.

Limitations

As far as we know, this is the first research that investigates whether women's sexual acts occur as a result of a desired action or exposure to power and authority, and raises awareness of women in society, who assume that sexuality is a duty that women should fulfill. The data of this study were collected to determine the views of women living in the north-west of Turkiye, as studies across Turkiye show that the rates of sexual violence are highest among women living in the north-east of the country. For this reason, it is accepted as a limitation of the research as it will affect the generalization of the results. Although progress has been made in sexuality in our country compared to the past years, unfortunately, sexuality is still seen as a taboo in our country. In this context, raising awareness about sexuality and sexual violence to women is a strong aspect of this study. On the other hand, it is another limitation that the findings on sexuality may lag behind the countries of the world.

Conclusion

At the end of the research, it was determined that women often perceived sexuality as a fundamental element for the continuation of marriage and commitment to their spouses. Participants stated that they were sometimes exposed to sexual violence and different types of violence in their sexual lives. In the present study, participants stated that they considered sexuality as a fundamental element for the continuation of marriage and spousal loyalty. Participants have also emphasized that men think differently about sexuality, and have argued that sexual intercourse turns into an act of violence in which women are sex objects

when there is no sexual desire between partners. In addition, some participants were exposed to verbal and psychological sexual violence. Sex education has become a basic necessity in Turkiye, which has a patriarchal society and where sexuality is considered taboo. Therefore, sex education should be provided to individuals through lifelong learning trainings starting from an early age. There is a need for further studies to examine different dimensions of this subject.

Authors Contribution

Study design: ECE, AK, Data collection: ECE, AK., Data analysis and interpretation: AK, ECE., Writing-Reviewing and Editing: AK, ECE., Drafting of the article: ECE, AK, Critical review: AK, ECE.

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Consent to Participate

The participant has consented to the submission to this journal.

Consent For Publication

The participant has consented to the submission to this journal.

Ethics Approval

The protocol for the research has been approved by Ethical permission for the study was obtained from Bartin University Social and Human Sciences Ethics Board (Date: 16.12.2021, Approval Number: 2021-SBB-0487).

Conflicts of Interest

The authors declare no competing interests.

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ORIGINAL ARTICLE

Factors Related to Levels of Burnout and Job Satisfaction in Family Physicians (Cross-sectional Research)

Aile Hekimlerinde Tükenmişlik ve İş Doyumu Düzeyleri ile İlişkili Faktörler (Kesitsel Araştırma)

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ABSTRACT

Aim: The study aims to evaluate the burnout and job satisfaction levels of family physicians in terms of some variables.
Method: The study is of cross-sectional type. It was held between 03.06.2019-03.09.2019. The sample was not selected in the study, the whole universe was tried to be reached. 255 family physicians working in Van province were included in the study. The participation rate is 82%.
Results: The mean scores of the participants of the study; Maslach sensuality: 29.87 ± 3.5, achievement: 23.62 ± 3.5, insensitivity: 13.37 ± 3.5, total: 22.29 ± 3.54, Minnesota total: 3.03 ± 0.68.
There is a significant difference between gender($p<0.04$), compliance with the personality structure of the study($p<0.04$), choosing the profession at its own will ($p<0.006$), presence of chronic illness($p<0.05$), physical and social conditions in the workplace($p<0.04$), and burnout scores.
Although there was no difference between the satisfaction of the family medicine system ($p<0.001$), the future anxiety of the system ($p<0.001$), and the burnout scores according to the satisfaction of the wage ($p<0.002$), there was a significant difference in terms of job satisfaction scores.
Conclusion: The study results show that family physicians feel from moderate to high levels of fatigue and emotional fatigue related to their profession. High scores in the depersonalization sub-dimension indicate that this situation is reflected negatively on the people they serve. It has been determined that thoughts about the family medicine system have an effect on job satisfaction rather than burnout.

Keywords: Family Practice; Burnout, Psychological; Job satisfaction, Cross-Sectional Studies

ÖZ

Amaç: Çalışmada aile hekimlerinin tükenmişlik ve iş doyumu düzeylerini bazı değişkenler açısından değerlendirmek amaçlanmıştır.
Yöntem: Çalışma kesitsel tiptedir. 03.06.2019-03.09.2019 tarihleri arasında yapılmıştır. Araştırmada örneklem seçilmemiş, evrenin tamamına ulaşılmaya çalışılmıştır. Çalışmaya Van ilinde çalışan 255 aile hekimi dahil edilmiştir. Katılma oranı % 82'dir.
Bulgular: Çalışmaya katılanların ölçek puan ortalamaları; Maslach duygusallık: 29.87±3.5, başarı: 23.62±3.5, duyarsızlaşma: 13.37±3.5, toplam: 22.29±3.54, Minesota toplam: 3.03±0.68'dir.
Cinsiyet ($p<0.04$), işinin kişilik yapısına uyması ($p<0.04$), mesleğini kendi isteği ile seçme ($p<0.006$), kronik hastalık varlığı ($p<0.05$), iş yerindeki fiziksel ve sosyal durumlarla ($p<0.04$) tükenmişlik puanları arasında anlamlı fark vardır.
Aile hekimliği sisteminden memnuniyet ($p<0.001$), sistemle ilgili gelecek kaygısı duyma ($p<0.001$) ve ücretten memnuniyet durumlarına ($p<0.02$) göre tükenmişlik puanları arasında fark olmamasına rağmen iş doyumu puanları açısından anlamlı fark vardı ($p<0.05$).
Sonuç: Çalışmanın sonuçları, aile hekimlerinin meslekleriyle ilgili orta ila yüksek düzeyde yorgunluk ve duygusal yorgunluk hissettiğini göstermektedir. Duyarsızlaşma alt boyutundaki yüksek puanlar, bu durumun hizmet ettikleri kişilere olumsuz yansıtıldığını göstermektedir. Aile hekimliği sistemi ile ilgili düşüncelerin tükenmişlikten ziyade iş tatmini üzerinde bir etkisi olduğu belirlenmiştir.

Anahtar Kelimeler: Aile Hekimliği; Tükenmişlik, Psikolojik; İş doyumu, Kesitsel çalışmalar

Introduction

Job satisfaction is an emotional reaction that occurs when the employee evaluates his job, working environment and workplace conditions. Job satisfaction is affected by personal characteristics such as age, gender, and education level, as well as organizational and environmental factors such as job content, wages, management policy and working conditions (1).

Burnout is the depletion of physical and mental resources. It occurs when we spend more energy than we take in (2). Burnout, first described by Freudenberger in 1974, often occurs in people who constantly work face-to-face with other people. Burnout in the individual begins with the first dimension called emotional exhaustion (fatigue, exhaustion) (3).

Emotional exhaustion refers to feeling exhausted from work (4). The second dimension involves developing negative and cynical attitudes towards other people and is called depersonalization. The third dimension is the person's negative evaluation of himself regarding work and feeling unsuccessful. Burnout is generally considered work stress and includes these three dimensions. Burnout occurs as emotional exhaustion and depersonalization increase and the sense of

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personal accomplishment decreases. Burnout causes consequences such as low job performance, constant absenteeism, and inability to fulfil work-related duties and is considered a social problem (5).

The workload of healthcare professionals can be heavy, especially when it comes to caring for terminally ill patients and providing emotional support. In addition, inadequacies in health services and imbalances in personnel distribution can create disappointment and tension. Work stress and burnout can lead to psychological effects (depression, anxiety) and physiological effects (headaches, muscle tension). Additionally, work-related tension can reduce productivity in the workplace, reduce job satisfaction, and cause staff loss (6).

In the health sector, the failure to compensate for mistakes, because the job requires attention and sensitivity, gives rise to the opinion that the professional satisfaction of health workers should be increased. It is expected that as employee satisfaction increases, job satisfaction will also increase and this will increase patients' satisfaction (7).

In this study, it was aimed to determine the burnout and job satisfaction levels of family physicians and to evaluate the burnout and job satisfaction levels in terms of some variables.

Material-Method

The study is of cross-sectional type. It was held between 03.06.2019-03.09.2019. The sample was not selected in the study, the whole universe was tried to be reached. 255 family physicians working in Van province were included in the study. The participation rate is 82%. Ethics committee approval was obtained for the study with the decision dated 01.11.2018 and numbered 2018/15 from the Regional Training and Research Hospital Clinical Research and Ethics Committee. Verbal informed consent was obtained from all participants included in the study. In this study, the necessary ethical requirements for human studies determined by the 2008 Helsinki Declaration were fulfilled.

In this study, a questionnaire prepared by the literature on the subject, the Maslach Burnout Scale (MBS) consisting of 22 items and the Minnesota Job Satisfaction Scale (MIS) consisting of 20 items were applied.

The validity and reliability study of MBS was carried out by Canan Ergin from Hacettepe University (8). MBS is a 22-item self-assessment scale consisting of three subsections: Emotional Exhaustion (EE), Depersonalization (D) and Lack of Personal Achievement (LPA). There are nine items in the EE subsection (Article no: 1,2,3,6, 13,14,16,20), five items in the D subsection (Item no:5,10,11,15,22), and eight items in the LPA subsection. Article (Article no: 4,7,12,17,18,19,21) is included. The options consist of five-point Likert-type questions (never, very rarely, sometimes, often, always). Questions belonging to the EE and D subsections of the MBS are negative while the questions belonging to the LPA subsection are positive. Therefore, high EE and D scores and low LPA scores indicate burnout.

The MIS validity and reliability study was conducted by Baycan in 1985 (9). MIS is a five-point Likert-type scale scored between 1 and 5. For the answer to each question, "I am not at all satisfied: 1 point, I am not satisfied: 2 points, I am undecided: 3 points, I am satisfied: 4 points, I am very satisfied: 5 points". All score averages are calculated as a value between 1.0 and 5.0. As a percentage value; 25% and below indicate low job satisfaction, 26-74% medium job satisfaction, and 75% and above indicate high job satisfaction (10).

Statistical Analysis

Data entry and analysis of the research were done with Van YYU Licensed SPSS 15.0 statistical program. Normal distribution was tested with Shapiro-Wilk. In the analysis of groups with two independent variables, the Student's t-test was used if parametric test conditions were met, and the Mann-Whitney U test was used if not. Spearman correlation test was used to evaluate the relationship between independent variables and scale scores, $p<0.05$ was considered significant. Means are given with standard deviation.

Results

41.6% (n=106) of the participants were female and 58.4% (n=149) were male. The mean age is 35±7.0, the total length of service is 9.78±7.3, and the average number of children is 1.86±1.0. 32.9% (n=84) of the participants were single, and 67.1% (n=171) were married. The spouses of 54.3% (n=93) of those married are working, and 12.9% (n=78) are not working. Of the family physicians, 91.4% (n=233) were general practitioners and 8.6% (n=22) were family physicians. 54.7% (n=127) of the general practitioners are considering specialization training. The average service period of the physicians is 9.78±7.3 years. The mean time they worked as family physicians were 5.0±2.8 years.

Family health centers classes are in five groups A, B, C, D, E. 20% (n=51) of the physicians were A class, 8.5% (n=22) B class, 5.6% (n=14) C class, 18% (n=46) D and 48% (122) of them work in an E-class family health center. There is a difference between Class A and Class B in terms of Maslach depersonalization scores. Those who work in class B have a higher score. There was no difference between the other classes. The physical condition of the workplace was evaluated as good, medium or bad. There was a difference between those who rated it as good and bad. Those who stated it as bad had a higher depersonalization score.

A weak positive correlation was found between the total length of service and Maslach achievement scores ($p=0.028$, $r=0.263$). There was a weak negative correlation between the Minnesota total score and the Maslach depersonalization scores ($p=0.025$, $r=0.269$)

Scale score averages of the participants in the study;

Table 1. Distribution of variables according to scale scores

			Maslach Scale (*Mean*±SD)								Minnesota Scale (*Mean*±SD)	
		n	Depersonalization score	p	Achievement score	p	Emotion score	p	Total score	P	Minnesota score	P
Gender	Female Male	106 149	14.06±3.3 12.87±3.7	0.173	24.10±3.6 23.29±3.5	0.352	31.72±5.3 28.56±6.2	0.030	23.29±3.26 21.57±3.59	0.044	3.08±0.67 2.99±0.69	0.58
Marital status	Single Married	84 171	13.69±4.1 13.21±3.3	0.600	23.13±4.4 23.87±3.0	0.478	30.34±7.6 29.63±5.1	0.649	22.39±4.50 22.24±3.02	0.869	2.83±0.54 3.13±0.72	0.082
Does the spouse work?	Yes No	220 35	13.36±3.4 12.55±3.0	0.514	23.97±3.2 23.44±2.0	0.644	29.44±5.5 30.44±3.5	0.512	22.26±3.26 22.14±1.78	0.886	3.15±0.76 3.04±0.55	0.690
Branch	Practitioner Family Physician	233 22	13.2±3.5 15.1±4.0	0.202	23.57±3.5 24.16±3.6	0.702	29.81±6.2 30.50±4.4	0.793	22.19±3.55 23.27±3.54	0.479	2.99±0.65 3.47±0.87	0.098
Specialization training contemplation?	Yes No	139 116	13.31±3.6 13.06±3.4	0.784	23.20±3.4 24.03±3.6	0.357	29.97±4.9 29.62±7.5	0.824	22.16±3.07 22.24±4.12	0.930	2.94±0.65 3.05±0.66	0.501
Does Your Job Match Your Personality?	Yes No	193 62	12.75±3.6 15.29±2.7	0.01	23.73±3.4 23.29±3.9	0.659	28.96±6.0 32.70±5.2	0.26	21.81±3.61 23.76±2.93	0.04	3.08±0.69 2.86±0.63	0.245
Did you choose your job voluntarily?	Yes No	193 62	12.65±3.4 16.00±2.7	0.001	23.18±3.5 25.26±3.2	0.04	29.25±6.3 32.13±4.4	0.10	21.69±3.56 24.46±2.50	0.006	3.11±0.67 2.74±0.64	0.06
Are you considering quitting your job?	Yes No	81 174	13.72±4.0 13.23±3.4	0.60	22.27±3.3 24.38±3.4	0.01	30.63±7.1 29.80±5.2	0.58	22.21±3.93 22.47±3.26	0.77	2.74±0.56 3.18±0.68	0.01
Do you have any chronic diseases?	Yes No	22 233	16.50±2.4 13.07±3.5	0.02	24.33±3.3 23.56±3.5	0.616	34.00±6.0 29.48±5.9	0.081	24.94±2.88 22.04±3.51	0.054	3.05±0.51 3.03±0.70	0.951
Do you have a physical defect?	Yes No	11 244	15.66±3.2 13.26±3.5	0.26	25.33±5.7 23.55±3.4	0.400	36.00±2.6 29.59±6.0	0.073	25.66±3.33 22.13±3.49	0.09	2.66±1.05 3.05±0.66	0.346
How is your socio-cultural environment at work?	Good Bad	106 149	12.51±3.3 13.97±3.6	0.094	23.20±3.1 23.92±3.8	0.409	28.34±4.8 30.95±6.6	0.076	21.35±2.61 22.95±3.97	0.047	3.30±0.76 2.84±0.55	0.004
Salary*	5-10 K over 10 K	124 131	12.35±3.6 14.33±3.2	0.020	23.55±3.6 23.69±3.5	0.875	29.76±6.3 29.97±5.8	0.887	21.89±3.73 22.66±3.35	0.364	2.85±0.67 3.20±0.66	0.03
Are you satisfied with the fee?	Yes No	41 29	13.68±3.2 12.93±3.9	0.391	23.85±3.3 23.31±3.8	0.533	30.07±5.6 29.58±6.6	0.743	22.53±3.19 21.94±4.01	0.494	3.18±0.74 2.81±0.52	0.023
Are you satisfied with the family medicine system?	Yes No	113 142	12.70±3.0 13.89±3.9	0.170	23.90±2.6 23.41±4.1	0.569	29.87±5.3 29.87±6.6	1.000	22.16±2.64 22.39±4.15	0.778	3.34±0.74 2.78±0.52	0.001
Do you have any future concerns about the family medicine system?	Yes No	215 40	13.54±3.5 12.454±3.7	0.359	23.69±3.7 23.27±1.9	0.582	29.91±6.1 29.63±5.9	0.890	22.38±3.63 21.78±3.10	0.612	2.95±0.65 3.47±0.68	0.019

Values in bold represent statistically significant results. The Student's t-test and the Mann-Whitney U test was used . * The specified numerical range is 25-50k and over 50k when adjusted according to 2024 inflation data.

Maslach emotionality: 29.87±3.5, achievement: 23.62±3.5, depersonalization: 13.37±3.5, total: 22.29±3.54, Minnesota total: 3.03±0.68. The distribution of independent variables according to scale scores is presented in Table 1.

There is a significant difference between emotional and total burnout scores according to gender. Emotional and total burnout scores are higher in women.

There is a significant difference between depersonalization and total burnout scores according to the fit of the job to the personality structure. Depersonalization and total burnout scores are significantly higher in those who say that the job does not fit their personality structure.

According to the answers given to the question "Did you choose your profession voluntarily," those who answered no have significantly higher burnout scores than those who answered yes.

Maslach achievement scores and Minnesota job satisfaction scores are significantly lower in those who are considering quitting their jobs than in those who do not.

Depersonalization scores are significantly higher in patients with chronic disease than those without.

Physicians with a good social environment at work have lower total burnout scores and higher job satisfaction scores.

Although depersonalization scores are higher in those with an income of over ₺ 10.000, there is no difference between the groups in terms of total burnout and job satisfaction scores.

Although there is no difference between burnout scores according to their satisfaction with the wage and family medicine system, job satisfaction scores are significantly higher in those who are satisfied with the wage and family medicine system.

There is no difference between burnout scores according to future anxiety about the family medicine system. Job satisfaction scores are significantly higher in those who are not worried about the future of the family medicine system.

Discussion

Burnout is one of the most common problems faced by employees in today's challenging business life. This situation is more common, especially in the field of health, where the workload is quite high.

Considering the burnout status of family physicians, emotional scores were 29.87±3.5, achievement scores 23.62±3.5, and depersonalization scores were 13.37±3.5. In a study conducted with family physicians, the mean emotional burnout score was calculated as 17.34±7.02, the personal achievement score as 9.96±4.30, and the depersonalization score as 4.93±4.06.11

In another study, the mean emotional exhaustion score of family physicians was calculated as 16.1±7.2, personal achievement score as 21.0±3.7, and depersonalization score as 4.3±3.2 (12). Subscale score distributions are similar to other studies. However, emotionality and depersonalization scores are higher than in other studies. Although no cutoff point is used for the assessment, the study results show that physicians experience high levels of burnout, considering that the upper values are 36 for emotional exhaustion, 20 for depersonalization, and 32 for a sense of personal accomplishment. The fact that the trait depersonalization sub-dimension score is higher than the scores obtained in other studies indicates that physicians reflect burnout in people who receive service.

In the studies examined in the literature, there are different results regarding the effect of gender and marital status on burnout. Some studies did not detect a difference according to gender, as well as studies that did (11-14) In our study, emotional and total burnout scores were significantly higher in women. There was no difference between burnout and job satisfaction scores according to my marital status. The difference in the studies may be due to the inclusion of assistant physicians or non-physician health personnel in the study.

There is no similar study evaluating job suitability for personality structure and burnout. In our study, it is noteworthy that depersonalization scores were high among those who indicated that their job was not suitable for their personality structure. In a study conducted with family physicians in Malatya, higher job satisfaction scores were observed among physicians who stated that their profession was compatible with their personality structure. Although job satisfaction scores were higher among those who reported job suitability for their personality in our study, no significant difference was found (15). This discrepancy may be attributed to the larger number of physicians participating in our study compared to other studies.

In a study conducted with family physician specialists, it was found that all burnout scores were higher in physicians who did not choose their profession voluntarily, which is consistent with our findings (16). Similarly, in our study, a difference was observed in general job satisfaction scores based on whether the profession was chosen willingly. Those who chose their profession willingly exhibited higher job satisfaction scores.

Another study with family physician specialists revealed higher depersonalization scores and lower personal achievement scores among those contemplating leaving their jobs. However, there was no difference in depersonalization and emotional exhaustion scores.

In the same study, it was observed that physicians considering leaving their jobs had lower job satisfaction scores. Similarly, in another study with family physicians, it was reported that those thinking of quitting their jobs had lower job satisfaction scores (15).

In a study conducted with family physicians in Kayseri, no difference was observed between having a diagnosed disease and burnout scores (12).

In studies conducted with family physicians, a difference was found between the physical conditions and working environment of the workplace and burnout scores. Those who reported inadequate physical conditions and working environment tended to have higher emotional exhaustion and depersonalization scores, and lower personal achievement scores (12,16). Unlike our study, there was no difference observed between workplace conditions and burnout scores. This difference may be attributed to the fact that classification was not considered in other studies.

In the study conducted with family physicians, the correlation between perceiving the salary as sufficient and burnout scores was examined, revealing a negative significant relationship only between emotional burnout score and salary adequacy (17). In another study with physicians, a significant difference was found between income sufficiency and personal achievement scores (16), while no difference was observed in emotional exhaustion and depersonalization scores (18). The literature review indicates varying results regarding wages and satisfaction with wages. In our study, a significant difference was found only in the depersonalization subscale score based on income level. Interestingly, physicians earning ₺10.000 or more showed higher depersonalization scores.

Considering the studies on wages and job satisfaction, a significant difference was found between income coverage and job satisfaction scores in the study conducted with physicians (15). In another study, it was reported that physicians who were satisfied with their salaries had higher job satisfaction scores (19). In a study with physicians working in primary care, it was observed that job satisfaction scores increased as the monthly income level increased (20). The results of our study suggest that factors such as salary and wage satisfaction have a greater impact on job satisfaction than burnout. Consistent with the literature findings, physicians with higher incomes who reported satisfaction with their pay had higher job satisfaction scores in our study.

In the study conducted with family physicians in Kayseri, the burnout scores of physicians who are satisfied with being in the family medicine system and who state that the practice meets their expectations decreased (12).

According to the study conducted in Sakarya, it was determined that there was a negative relationship between the positive perception of the family medicine system and burnout (17).

In studies conducted with family physicians in Eskişehir and Malatya, it has been reported that physicians who are satisfied with the family medicine system have higher job satisfaction scores (15).

It has been determined that the situations related to the system are most effective on job satisfaction. In our study, family physicians who are satisfied with the system and are not worried about the future of the system have higher job satisfaction scores.

Conclusion

Study results; suggest that family physicians may experience moderate-to-high levels of professional fatigue and emotional strain, and commuting to work is a source of anxiety. Remarkably, the high scores in the depersonalization sub-dimension indicate that this situation is reflected negatively on the people they serve. Unlike other studies, it has been determined that conditions such as monthly income, satisfaction with the wage satisfaction with the family medicine system, and worrying about the future of the system have an effect on job satisfaction rather than burnout. The job satisfaction score of the majority of physicians is moderate. It seems important to make institutional arrangements for the preparation of conditions that protect and maintain the mental health of the employees to reduce the emotional attrition of the physicians working in primary care, to increase job satisfaction, and to increase the quality of the services provided.

Ethical approval: Ethics committee approval was obtained for the study with the decision dated 01.11.2018 and numbered 2018/15 from the Regional Training and Research Hospital Clinical Research and Ethics Committee

Informed Consent: Verbal informed consent was obtained from all participants in this study.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORIGINAL ARTICLE

Collection and Transplantation of Peripheral Blood Stem Cells in Children: A Single-Center Experience

Çocuklarda Periferik Kan Kök Hücrelerin Toplanması ve Transplantasyonu: Tek Merkez Deneyimi

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ABSTRACT

Background/Aims: As a source of hematopoietic stem cells, peripheral blood stem cells have been used more frequently in both malignant and non-malignant diseases. There are some difficulties in the collection of peripheral blood stem cells (PBSC) from children compared to adults such as vascular access and extracorporeal circuit volume, especially in small children.
Methods: In this study, we present our experience in 63 children who underwent peripheral blood stem cell collection and transplantation between November 2016 and September 2023.
Results: The median age and weight of the children at the time of apheresis procedures were 10.25 years and 34 kg, respectively. Of 63 peripheral blood stem cell collection and transplantations, 48 were autologous and 15 were allogeneic. The median cell yield per apheresis procedure was 2.6 x 106 CD34+ cells/kg (0.6-9.66). Four of the total 63 patients and donors required multiple apheresis procedures. No significant side effects were observed after apheresis procedures.
Conclusion: We observed that in experienced hands, peripheral blood stem cell collection and transplantation in children is at least as safe and effective as in adults.

Keywords: bone marrow transplantation, hematopoietic stem cell transplantation, peripheral stem cell transplantation, children

ÖZ

Amaç: Hematopoetik kök hücre kaynağı olarak periferik kan kök hücreleri hem malign hem de non-malign hastalıklarda giderek daha çok kullanılmaktadır. Ancak çocuklarda özellikle de küçük çocuklarda erişkinlerden farklı olarak periferik kan kök hücre toplanmasında damar yolu ve ekstrakorporeal set volümü gibi zorluklarla karşılaşılabilmektedir.
Yöntem: Biz bu çalışmada Kasım 2016 ile Eylül 2023 tarihleri arasında, kendi merkezimizde periferik kan kök hücre toplaması ve transplantasyonu yaptığımız 63 çocuk hastayı sunuyoruz.
Bulgular: Aferez seansları sırasında çocukların ortalama yaş ve kiloları sırasıyla 10.25 ve 34 kg idi. Toplam 63 periferik kan kök hücre toplanması ve transplantasyonu işleminin 48'i otolog, 15'i allojeneik idi. Her aferez seansında elde edilen ortalama kök hücre sayısı 2.6 x 106 CD34+ hücre/kg (0.6-9.66) idi. Toplam 63 hasta ve donordan 4'üne multipl aferez seansları gerekti. Aferez seansları sonrası önemli bir yan etki gözlenmedi.
Sonuç: Deneyimli ellerde, çocuklarda periferik kan kök hücre toplaması ve transplantasyonunun en az erişkinler kadar güvenli ve etkili olduğunu gözlemledik.

Anahtar Kelimeler: kemik iliği nakli, hematopoetik kök hücre nakli, periferik kök hücre nakli, çocuklar

Introduction

Bone marrow transplantation (BMT), also known as hematopoietic stem cell transplantation (HSCT), currently uses bone marrow, peripheral blood, or umbilical cord as stem cell sources. BMT is used in hematological malignancies as well as hemoglobinopathies, immunodeficiencies, bone marrow failure, and inborn metabolic diseases (1). In recent years, the number of HSCTs using peripheral blood stem cell (PBSC) and cord blood has been increasing in children (2). Initial trials of PBSC transplantation had been performed mainly in adult patients, and there had been only a few reports in small children. However, over time, there has been an increasing trend in pediatric patients. Initially, the collection of PBSC in children was performed generally in younger cancer patients for autologous use, but in the course of time, beside autologous usage, more and more healthy children have been donating PBSC via apheresis for use by their ill siblings (3-5). There is a limited number of studies on the collection procedures, collection efficacy, and donor safety of PBSC in children. Here, we reviewed our records of 63 children who underwent apheresis procedures for PBSC collection out of 120 stem cell harvesting procedures performed in 115 children in our pediatric HSCT center.

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Material-Method

We retrospectively reviewed autologous and allogeneic PBSC collection procedures performed in our Pediatric Bone Marrow Transplant Unit between November 2016 and September 2023. All donors were medically evaluated before mobilization and collection. Written informed consent was obtained from the families of the donors before the procedures. The study was approved by the ethics committee of our hospital (2023/233).

PBSC mobilization was performed using granulocyte colony-stimulating factor (G-CSF) alone or in combination with plerixafor. G-CSF was administered as a single daily dose of 5 µg/kg for 5 consecutive days. Collection was performed on the 5th day. The targeted CD34+ cell count was determined as 2 x 106 CD34+ cells/kg. The additional doses of G-CSF were administered in cases that required a second or third dose of apheresis.

In all cases, PBSC collection was performed using a central venous catheter. The right jugular vein was preferred for central venous catheter applications. Access was obtained via a 7 French (for donors <20 kg) or 9 French (for donors ≥20 kg) central venous dialysis catheter (Medcomp, Harleysville, PA, US) with double lumens. Central venous catheter placement was performed under general anesthesia. In patients <25 kg, the extracorporeal line was primed with red blood cells to mitigate hemodynamic complications.

Mild sedation with hydroxyzine was administered to agitated patients during apheresis, and the blood pressure, oxygen saturation, and heart rate values of all donors were monitored throughout the apheresis procedure.

All collection procedures were performed using an AS.TEC204 (Fresenius NPBI, Dreieich, Germany) blood cell separator under manual control, via a P1Y disposable tubing set with an extracorporeal volume of 176 ml. A solution of 500 mL acid-citrate-dextrose (ACD-A) without heparin was infused at a whole blood to anticoagulant ratio of 1:15 for anticoagulation.

Results

The median age of the donors was 10.25 years (range: 3-18 years) and their median weight was 34 kg. The donor with the lowest weight of 14 kg was a 3-year-old child with stage IV neuroblastoma. The youngest donor was the same patient. The median body surface area of the donors was 1.16 m2 (range: 0.66-1.88). The median body mass index of the donors was 19.3 m2 (range: 12.2-25.4) (Table 1).

The indications and stem cell sources of our total 120 HSCTs in 115 children since 2016 are summarized in Table 2. Among these 120 HSCTs, 63 (52.5 %) were PBSC-derived. Most of the HSCTs which were PBSC-derived were performed with the diagnosis of solid malignancies (52 of 63 PBSC-derived transplantations, 82.5%). Among the 63 PBSC-derived transplants, 15 (24%) were allogeneic grafts from healthy siblings of patients under 18-year-old with parental consent, and 48 (76%) were autologous grafts (Table 3). One of the autologous graft cases was both PBSC and bone marrow-derived, and the procedure was performed for the diagnosis of acute myeloid leukemia. The characteristics of the donors who underwent apheresis procedures for PBSC collection are summarized in Table 1. Among the 63 PBSC-derived transplant cases, 51.,7% were boys, and 48.3% were girls.

Characteristics of the PBSC apheresis procedures, the pre-apheresis peripheral blood leukocyte counts of the donors, and their pre-apheresis polymorphonuclear leukocyte counts are given in Table 1. The median blood flow rate was 50 ml/min (range: 14-70). The median CD34+ cell yield was 2.6 x 106/kg (range: 0.6-9.66) after one apheresis procedure. The procedures had a median duration of 110 minutes. No significant adverse events related to apheresis were observed. Only 4 of the 63 patients (6.3%) required additional apheresis procedures. The characteristics of the donors who needed two or more mobilization procedures are summarized in Table 4 and 5. One of these cases was a 10-year-old girl diagnosed with neuroblastoma whose CD34+ hematopoietic stem cells count was 0.8 x 106/kg after purging in the first collection process. Her second collection process was performed after mobilization with G-CSF and plerixafor. Her CD34+ hematopoietic stem cells count was 5.3 x 106/kg after the second procedure.

Table 1. Characteristics of the donors who underwent apheresis procedures for PBSC collection and characteristics of PBSC apheresis procedures [a,b]

Parameters	Values
Donor characteristics	
Age (years)	10.25 (3-18)
Sex	
Male/Female	32 (51.7%)/31 (48.3%)
Weight (kg)	34 (14-77)
Height (cm)	137 (100-176)
BSA (m^2)	1.16 (0.6-1.88)
BMI (kg/m^2)	19.3 (12.2-25.4)
Leukocyte count ($x10^9/L$)	36 (20-60.2)
PMNL counts ($x10^9/L$)	30 (11.7-55)
Characteristics of PBSC apheresis procedures and products	
Blood volume of donors (ml)	2800 (1120-5600)
Volume of blood processed (ml)	7000 (2500-11250)
Apheresis time (min) Blood flow rate (ml/min)	110 (90-240) 50 (14-70)
Product volume (ml)	200 (110-890)
Product leukocyte count ($x10^9/L$)	150.4 (45-280)
CD34 (%)	0.29 (0.1-0.86)
CD34 ($10^6/kg$)	2.6 (0.6-9.66)

Data are presented as frequency (percentage) and median (min-max) values.

PBSC, peripheral blood stem cells; BSA, body surface area; BMI, body mass index; PMNL, polymorphonuclear leukocyte, CD, cluster of differentiation

a Total PBSC-derived HSCT count: 63

b Total PBSC apheresis procedure count:113

PBSC apheresis procedure count per HSCT: 1-4 times

Table 2. Indications and stem cell sources of HSCTs [a,b]

Parameters	Values				
Indications	Stem cell sources				Total
	PBSC	BM	PBSC+BM	BM+UCB	
Neuroblastoma [c]	21(17.50%)	3 (2.50%)			24 (20.00%)
Thalassemia major		13 (10.83%)		1 (0.83%)	14 (11.66%)
AML [c]	3 (2.50%)	9 (7.50%)	1 (0.83%)		13 (10.83%)
NHL	6 (5.00%)	7 (5.83%)			13 (10.83%)
ALL [c]	3 (2.50%)	9 (7.50%)			12 (10.00%)
HL [c]	12 (10.00%)				12 (10.00%)
FAA		4 (3.40%)			4 (3.40%)
LCH	2 (1.66%)	1 (0.83%)			3 (2.50%)
PNET	3 (2.50%)				3 (2.50%)
Ewing sarcoma	3 (2.50%)				3 (2.50%)
CML		3 (2.50%)			3 (2.50%)
MDS	1 (0.83%)	1 (0.83%)			2 (1.66%)
SCID	1 (0.83%)	1 (0.83%)			2 (1.66%)
JMML	1 (0.83%)	1 (0.83%)			2 (1.66%)
BPDCN [c]	1 (0.83%)	1 (0.83%)			2 (1.66%)
Osteopetrorickets	1 (0.83%)				1 (0.83%)
Germ cell tumor	1 (0.83%)				1 (0.83%)
Griscelli syndrome		1 (0.83%)			1 (0.83%)
Aplastic anemia		1 (0.83%)			1 (0.83%)
Wilm'erm cell tumor(FR (for donors Gürsel, Oğuzhan Babacan, Vural Kesik, Emin Kürekçis tumor	1 (0.83%)				1 (0.83%)
FAA+AML	1 (0.83%)				1 (0.83%)
WAS	1 (0.83%)				1 (0.83%)
AML+ALL	1 (0.83%)				1 (0.83%)
Total	63 (52.50%)	55 (45.88%)	1 (0.83%)	1 (0.83%)	120 (100%)

Data are presented as frequency (percentage) values.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; LCH, Langerhans cell histiocytosis; PNET, primitive neuroectodermal tumor; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; SCID, severe combined immunodeficiency; JMML, juvenile myelomonocytic leukemia; FAA, Fanconi aplastic anemia; WAS, Wiskott-Aldrich syndrome; BPDCN, blastic plasmacytoid dendritic cell neoplasm; BM, bone marrow; PBSC, peripheral blood hematopoietic stem cells; UCB, umbilical cord blood

[a] Total patient count:115

[b] Total hemopoietic stem cell transplantations:120

[c] One of the ALL patients underwent 2 allogeneic PBSC-derived HSCT procedures; One of the HL patients underwent 1 autologous PBSC-derived HSCT procedure, and 1 allogeneic PBSC-derived HSCT procedure; One of the neuroblastoma patients underwent 2 autologous PBSC-derived HSCT procedures; One of the AML patients underwent 2 allogeneic bone marrow-derived HSCT procedures; The BPDCN patient underwent 1 autologous PBSC-derived HSCT procedure and, 1 allogeneic bone marrow-derived HSCT procedure.

Table 3. Donor types of HSCTs

Parameters	Values				
	Stem cell sources				
Type of transplantation	PBSC	BM	PBSC+BM	BM+UCB	Total
Autologous [c]	48 (40.00%)	4 (3.33%)	1 (0.83%)		53 (44.17%)
Allogeneic [c]					67 (55.83%)
Full-matched	14 (11.67%)	50 (41.67%)		1 (0.83%)	65 (54.17%)
Well-matched	1 (0.83%)	1 (0.83%)			2 (1.67%)
Total	63 (52.50%)	55 (45.83%)	1 (0.83%)	1 (0.83%)	120 (100%)

Data are presented as frequency (percentage) values.

HSCT, hematopoietic stem cell transplantation; BM, bone marrow; PBSC, peripheral blood hematopoietic stem cells, UCB; umbilical cord blood

[a] Total patient count: 115

[b] Total hemopoietic stem cell transplantations: 120

[c] One of the ALL patients underwent 2 allogeneic PBSC-derived HSCT procedures; One of the HL patients underwent 1 autologous PBSC-derived HSCT procedure and, 1 allogeneic PBSC-derived HSCT procedure; One of the neuroblastoma patients underwent 2 autologous PBSC-derived HSCT procedure; One of the AML patients underwent 2 allogeneic bone marrow-derived HSCT procedure; The BPDCN patient underwent 1 autologous PBSC-derived HSCT procedure and, 1 allogeneic bone marrow-derived HSCT procedure.

Table 5. Characteristics of allogeneic donors who needed two or more mobilization procedures

Parameters First PBSC apheresis Second PBSC apheresis[a]					Hours after the start of PBSC apheresis CD34+ results as 10^6/kg of recipient weight			
Patient Sex (F/M)	Patient age (year)	Donor age (year) / Sex (F/M)	Diagnosis	Disease status	96 hours	144 hours	96 hours	P
M	15	17/M	AML	Relapse	4.4	3.47	2.78	9.04
M	17	16/F	ALL	Relapse	6.67	-	5.7	5.04

PBSC, peripheral blood hematopoietic stem cells; CD, cluster of differentiation; F, female; M, male; P, after purging; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia

a There was one month between the two PBSC apheresis procedures for the first patient; There were two months between the two PBSC apheresis procedures for the second patient.

Table 4. Characteristics of autologous donors who needed two or more mobilization procedures

Parameters First PBSC apheresis						Hours after the start of PBSC apheresis CD34+ results as 10^6/kg of recipient weight									
						Second PBSC apheresis[a]									
Sex (F/M)	Age (year)	Diagnosis	Disease status	Stage	CT cycles	72 hours	96 hours	120 hours	144 hours	P	PLX +/-	72 hours	96 hours	120 hours	P
F	10	NBL	Primary	IV	3-4 courses	0.4	1.4	-	-	0.8	+	-	-	9.7	5.3
M	14	NBL	Relapse	IV	6-course ICE + 3-course TCV	0.9	3.8	3.5	2	1.8	-	2.7	1.9	-	1.8

PBSC, peripheral blood hematopoietic stem cells; CD, cluster of differentiation; F, female; M, male; P, after purging; CT, chemotherapy; PLX, Plerixafor; NBL, neuroblastoma; TCV, Topotecan-cyclophosphamide-vincristine; ICE, ifosfamide carboplatin etoposide

a There was one month between the two PBSC apheresis procedures for the first patient; There were two months between the two PBSC apheresis procedures for the second patient.

Discussion

After 1968, bone marrow had been used for hematopoietic stem cell collection for a very long time. However, PBSC transplantation using G-CSF for stem cell mobilization began in the early 2000s, and the use of both autologous and allogeneic PBSC has gradually increased worldwide (6,7). According to data from the European Group for Blood and Marrow Transplantation registry (EBMT), pediatric recipients undergoing transplantations from any donor received bone marrow in 64% of the cases, PBSCs in 30% and umbilical cord blood in 6% of the cases (8, 9).

It has been reported that successful PBSC collection can be performed with G-CSF even in children weighing 10-15 kg without any significant complication (10). In fact, Nussbaumer et al. reported successful PBSC mobilization and collection procedures in 3 neuroblastoma patients under 10 kg (11). In this study, we showed that the mobilization and collection of PBSC in pediatric donors are a safe and effective procedures in expert hands. However, the priming of the extracorporeal separator line with red blood cells or albumin, as we did, has been recommended to ensure hemodynamic tolerance and a more effective collection process in such children.

The greatest advantage of PBSC transplantation over BMT is that neutrophil and platelet engraftment occurs in a shorter period of time, which results in fewer infection problems, shorter hospitalization periods and less need for transfusion (1). Perhaps, a disadvantage may be an increased risk of chronic graft-versus-host disease (12). This may be caused by the presence of mature T lymphocytes in the peripheral blood or the drugs used during the conditioning regime (13, 14). From a procedural point of view, potential advantages of PBSC collection include the absence of need for general anesthesia and post-BM harvest hospitalization, less physical difficulty, and less emotional stress. On the other hand, the collection procedure in children is more difficult than that in adults because of the low blood volume in the former, the high extracorporeal volume of disposable materials, the usage anticoagulants, particular problems related to the achievement of appropriate venous access, and side effects of the drugs used in mobilization (6, 15-18).

Normally, the amount of PBSC in the circulating blood is very low. However, this amount can be significantly increased by chemotherapy, applications of sequential growth factors applications such as G-CSF, and some signaling pathway inhibitors such as plerixafor (19, 20). We used G-CSF and plerixafor in our patients. For adequate CD34+ cell collection in PBSC transplantations, EBMT recommends the use of a single daily dose of 10 mg/kg of G-CSF (8). Nevertheless, we obtained sufficient stem cell counts in 59 of our 63 donors (93.6%) using G-CSF at a dose of 5 mg/kg/day. There are also different methods of using G-CSF in the literature (21). In recent years, the use of plerixafor has become increasingly common in patients who do not respond adequately to G-CSF treatment (22). The target stem cell count for the collection and infusion of PBSC in pediatric patients is a minimum of 2 x 106 CD34+ cells/kg (23). This level is 5 x 106 CD34+ cells/kg for adult patients (23, 24). In our patients, this level was adequate at an average of 2.6 x 106 CD34+ cells/kg. It has been demonstrated that younger age, more days of apheresis, and male gender are predictive of higher cell yields (16,19,20).

One of the most important issues when performing apheresis in children is that pediatric patients must have adequate hemoglobin and platelet counts. These levels have been reported as at least 12 g/dL hemoglobin and 40 x 109/L platelets for low-weight children (20,21,25,26).

The adverse effects of PBSC in donors are usually mild and minor. G-CSF-induced pain has been reported in less than 15% of pediatric donors (8,16,20). We observed headaches accompanied by low-grade fever and bone pain in 10% of patients after G-CSF use, and all of these symptoms were transient. If we had used G-CSF at higher doses such as 10 mg/kg/day, we might have encountered more side effects. Capillary leak syndrome, pericarditis, hypercalcemia, hypertension, hypotension and dyspnea accompanied by hypoxia, nausea and diarrhea, back pain and thrombocytopenia are other side effects reported in the literature in PBSC studies (1). These complications were reported to have been associated with the number of apheresis procedures (1). Depending on the condition of the patient or the underlying disease, the number of apheresis procedures usually varies between 1 and 3 (27). We performed multiple apheresis procedures in only 4 of our 63 patients.

The most commonly used anticoagulants during apheresis procedures are ACD-A or heparin. Some centers may use both simultaneously (28). The most important side effect of ACD-A use is citrate-induced hypocalcemia (28). We used ACD-A as an anticoagulant in our patients and did not encounter any side effects.

Study Limitations

The first limitation of our study was the limited number of patients. Secondly, we did not differentiate age and sex in terms of the PBSC counts after PBSC collection.

Conclusion

Although apheresis in children is technically similar to that performed in adults, some physicians are concerned about performing apheresis on children. However, previous studies and our study have shown that when this procedure is performed by an experienced team, it is safe, and sufficient counts of PBSC are obtained for autologous or allogeneic HSCTs.

Author Contributions

Conception: C.Z., O.G., İ.E., E.A., A.E.K, Data Collection and Processing: C.Z., A.B., O.G., İ.E., E.A., A.E.K., Design: O.G., İ.E., E.A., A.E.K., Supervision: O.G., E.A., Analysis

and Interpretation: C.Z., O.G., A.B., Literature Review: C.Z., Writer: C.Z., Critical Review: O.G.

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ORIGINAL ARTICLE

Uncovering the Risks: Investigating the Impact of Abnormal 50 g Results of Two-Step Gestational Diabetes Mellitus Screening in Pregnant Women

Risklerin Ortaya Çıkarılması: Gebe Kadınlarda İki Adımlı Gestasyonel Diabetes Mellitus Taramasının Anormal 50 gr Sonuçlarının Araştırılması

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ABSTRACT

Background/Aims: Gestational Diabetes Mellitus (GDM) is a prevalent medical concern among pregnant women. The study aimed to explore maternal characteristics that could lead to an isolated increase in the 50 g Glucose Challenge Test (GCT) levels and to assess the impact of elevated 50 g GCT levels on fetal and neonatal outcomes.
Methods: This retrospective trial included 177 pregnant women and 177 infants. All pregnant women who applied to the antenatal clinic and screened for GDM were included in the study. Patients were divided into two groups: patients with abnormal GCT (50 g levels) but normal 100 g-OGTT results (study group) and those with normal 50 g results (control group).
Results: The advanced maternal age (AMA) rate (14.80% vs. 4.80%, p=0.028) and maternal weight measurements at the first pregnancy visit were higher in the study group. The rate of overweighted patients (more than 80 kg at the first pregnancy visit) was higher in the study group (35.20% vs. 5.80%, p<0.001). The rate of fetal macrosomia was higher in the study group (10.20% vs. 0, p<0.05). It was determined that the neonate's head circumference (HC) was larger in the study group (35.15 cm vs. 34.69 cm, p=0.029). Emergent (primary) cesarean section (C/S) rate with cephalopelvic disproportion (CPD) indication was higher in the fetal macrosomia group (p<0.05). The power of the current study was determined as 87%
Conclusions: According to the study result, the patients with isolated elevation of the 50 g Glucose Challenge Test are at risk of fetal macrosomia, which increases the risk of C/S. In overweight patients over 35 years old, 75 g OGTT may be more sensitive in detecting glucose metabolism disorders.

Keywords: Macrosomia, screening, cephalopelvic disproportion, primary cesarean section rate.

ÖZ

Amaç: Gestasyonel Diabetes Mellitus (GDM) hamile kadınlar arasında yaygın görülen bir tıbbi sorundur. GDM'nin zamanında tanımlanması ve yönetimi, anne ve fetusa ait komplikasyon potansiyelini azaltabilir. Bu çalışmanın amacı, Glukoz Challenge Testi (GCT) 50 gr düzeyi yüksek olup, ancak 100 gr OGTT sonuçları normal olan hastalarda, 50 gr düzeyinin yüksekliğine neden olabilecek anne özelliklerini araştırmak ve bu yüksekliğin fetal ve neonatal sonuçlar üzerindeki etkisini değerlendirmektir.
Gereç ve Yöntemler: Bu retrospektif çalışmaya 177 hamile kadın ve 177 yenidoğan dahil edildi. Doğum öncesi kliniğine başvuran GDM taraması yapılan tüm gebelerin sonuçları incelendi. Hastalar iki gruba ayrıldı: anormal GCT (50 gr düzeyleri) olup, ancak 100 gr-OGTT sonuçları normal olan hastalar (çalışma grubu) ve normal 50 gr sonuçları olan hastalar (kontrol grubu).
Bulgular: İleri anne yaşı (AMA) gözlenen hasta oranı çalışma grubunda daha yüksekti. (%14,80 vs. %4,80, p=0,028). İlk trimester maternal kilosu ölçümlerinde gruplar arasında fark vardı. Aşırı kilolu (ilk gebelik muayenesinde 80 kg'ın üzerinde) hasta oranı çalışma grubunda daha yüksekti (%35,20 vs. %5,80, p<0,001). Çalışma grubunda fetal makrozomi oranı daha yüksekti (%10,20 vs. 0, p<0,05). Yenidoğanın baş çevresinin (HC) çalışma grubunda daha büyük olduğu belirlendi (35,15 cm vs. 34,69 cm, p=0,029). Baş-pelvik uyumsuzluk (CPD) endikasyonu ile acil (primer) sezaryen (C/S) oranının fetal makrozominin tespit edilen hastalarda daha yüksek olduğu belirlendi (p<0,05). Gerçekleştirilen güç analizi sonucunda mevcut çalışmanın gücü %87 olarak belirlendi
Sonuç: Çalışma sonucuna göre, çalışma grubundaki hastalar fetal makrozomi açısından risk altındadır ve bu da sezaryen riskini artırmaktadır. Aşırı kilolu ve 35 yaş üstü hastalarda 75 gr OGTT glukoz metabolizması bozukluklarının tespitinde daha duyarlı olabileceği düşünmekteyiz.

Anahtar Kelimeler: Makrozomi, tarama, baş-pelvik uyumsuzluğu, primer sezaryen oranı.

Introduction

Gestational Diabetes Mellitus (GDM) is a form of impaired glucose tolerance diagnosed for the first time during pregnancy (1). According to "Coustan and Carpenter," diagnostic criteria in a study conducted in Turkiye, the prevalence of GDM in pregnant women was 9.2% (2). It affects a significant number of pregnant women, with prevalence rates varying based on factors such as race, diagnostic methods and gestational age at screening (3). There are various screening methods for GDM, but no consensus on diagnostic criteria has been established. Screening for GDM can be done using either a single-step or double-step method. The single-step (75 g oral glucose tolerance test -OGTT) screening was performed with 75 g glucose. In the double-step screening, the glucose level is checked one hour after the 50 g glucose load (50 g glucose challenge test-GCT), regardless of the fasting status, and if it is above the threshold value, a three-hour 100 g oral (glucose tolerance test-OGTT) is performed.

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The complications related to the fetus and the mother in patients diagnosed with GDM should be taken seriously. The most common pathological conditions are preeclampsia, gestational hypertension, polyhydramnios, macrosomia, increased risk of birth trauma, shoulder dystocia, perinatal mortality, increased operative birth rate (cesarean section (C/S) and instrumental delivery), fetal cardiomyopathy, neonatal respiratory and metabolic problems (hypoglycemia, hypocalcemia) (4). Close monitoring and treatment of GDM and abnormal serum glucose levels can reduce adverse effects on the mother's health and neonate complications.

This study aims to define patients with abnormal 50 g glucose challenge test (GCT) results but normal 100 g oral glucose tolerance test (OGTT) results, and to determine maternal characteristics that may relate to this condition. Additionally, study's objective is to diagnose and identify an isolated increase in the 50 g level of GCT, and its impact on fetal and newborn outcomes.

Material and Methods

This retrospective study was conducted in our hospital between 01.01.2020 and 01.01.2021. (Approved Number: 2020-9/8). We included all patients who gave birth in our hospital and were scanned for GDM. All pregnant women attending the antenatal clinic were offered screening for GDM, which was done with two-step screening at 24–28 weeks of gestation. In the first screening step, if the patients had plasma glucose levels more than > 135 mg/dl (7.5 mmol/l) in GCT, they were scanned with 100 g OGTT (5, 6). Patients with glucose levels ≥ 183 mg / dL (10.2 mmol/l) of GCT were considered diabetic and excluded from the trial. If screens are positive following STEP-I, a diagnostic test, with a 100 g 3-hour oral glucose tolerance test (OGTT), is performed. If at least two values were exceeded, GDM was diagnosed, and these patients were also excluded from the dataset. Women with an abnormal level of GCT (50 g) and nondiabetic 100 g OGTT results were included in our study. Pregnant women who did not consent to screen, and those who did not give birth in our hospital were excluded from the study. The patients were divided into two groups based on the results of 50g by using the consecutive sampling method: patients with abnormal GCT (50 g levels) but normal 100 g-OGTT results (study group) and those with normal 50 g results (control group). In the present study, the group of patients with an abnormal GCT (50 g) results at the two-step screening who were not diagnosed with GDM was defined as the study group. There were 88 patients in the study group and 89 in the control group. The control group included patients with normal results of GCT (50 g) (Figure 1). Maternal demographic and obstetric characteristics were analyzed. Those were maternal age (advanced maternal age more than 35 (AMA), gravida, parity, initial weight (overweighted pregnancy defined as weight ≥ 80 kg), gestational weight gain (GWG) from randomization to delivery (in kilograms), gestational hypertension, preterm birth (23 weeks <PTB <37 weeks), cesarean section history (planned C/S) and primary C/S rate (during labor).

The primary outcomes were fetal, and the secondary outcomes were neonatal. Fetal outcomes were pathological conditions diagnosed in the current pregnancy: macrosomia (i.e., LGA or birth weight> 4000 g), polyhydramnios, small for gestational age (SGA), and fetal anomalies. Neonatal outcomes were: Apgar scores, neonatal anthropometric parameters (infant birth weight (BW), and head circumference (HC), birth weight (i.e., birth weight> 4000 g), clinically diagnosed neonatal hypoglycemia, hyperbilirubinemia and neonatal hospitalization rate.

Statistical Analysis

Considering the overall macrosomia rates in the 50 g high (p1= 10.20%, n=9/88) and control (p2=0, n=0/89) group, the current post hoc power of the study was calculated as 87% for α=0.05. G*Power v.3.1.9.6 software was used. The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation if they followed the normal distribution and median (minimum: maximum) values if they did not fit the normal distribution. The Mann-Whitney U test independent sample t-test and ANOVA test were used for between-group comparisons. Categorical variables were compared using Chi-Square, Fisher's Exact, and Fisher-Freeman-Halton Test. Multivariable logistic regression analysis was applied to determine the risk factors affecting the 50 g level. SPPS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used to perform the statistical analysis. A $p < 0.05$ was considered statistically significant.

Results

In total, 177 pregnant and 177 infants were included in the study. The mean age of the pregnant was 27.78 ± 5.07 years. The mean gestational age of the infant was 38.84±1.46 weeks, and the birth weight was 3382.38 ± 497.73 grams.

It was determined that the median age was higher in the study group (29 years vs. 26 years, $p<0.001$) (Table-1). The proportion of participants aged ≥35 years was higher in the study group than in the control group (17% vs. 5.60%, p=0.016) (Table-1). There was no difference between groups in terms of gravida and parity numbers (p=0.487 and p=0.282); abortion rates also did not differ between groups (p=0.131) (Table-1). There was no difference between the groups according to the history of the (C/S) in previous pregnancies (p=0.125) (Table-1). Type of delivery, previous cesarean section history and C/S with cephalopelvic disproportion (CPD) indications did not differ between the groups (p=0.198) (Table-1).

There was a difference between the groups in maternal weight measurements at the first pregnancy visit (initial weight) (Table-1). The median maternal weight measurement was higher in the study group

Table 1. Comparison of demographic and obstetric characteristics, weight, and fasting plasma glucose levels.

	50g levels				
	n	Study group	n	Control group	p-value
Age (years)	88	29(20:42)	89	26(18:41)	<0.001[a]
<35 years	88	73(80%)	89	84(94.40%)	0.016[b]
≥35 years		15(17%)		5(5.60%)	
Gravida	88	2(1:6)	88	2(1:5)	0.487[a]
Parity	88	1(0:5)	88	1(0:3)	0.282[a]
Abortus	88	9(10.20%)	88	16(18.20%)	0.131[b]
C/S History	88	28(31.80%)	88	19(21.60%)	0.125[b]
Type of birth					
Vaginal Delivery	88	43(48.90%)	89	53(59.60%)	0.198[b]
C/S (previous pregnancy)		28(31.80%)		18(20.20%)	
C/S (primary)		17(19.30%)		18(20.20%)	
Initial weight (kg)	86	68(47:92)	85	64(45:95)	0.010[a]
Third-trimester weight (kg)	85	79.26±11.04	85	78.20±11.04	0.532[c]
Gestational Weight Gain (kg)	85	10(-3:25)	82	13(2:27)	<0.001[a]
Overweight Pregnancy	88	31(35.20%)	86	5(5.80%)	<0.001[b]
Fasting glycemia	88	84(55:151)	89	84(66:124)	0.851[a]

Data were presented as median (minimum: maximum), mean ± st. deviation and n%.
a: Mann Whitney U Test, b: Chi-Square Test, c: Independent Samples t-Test, d: Fisher-Freeman-Halton Test

Table 2. Comparison of perinatal, and neonatal characteristics.

	50g levels				
	n	Study group	n	Control group	p-value
Perinatal Pathology	88		89		0.005[d]
Polyhydramnios		5(5.70%)		3(4.50%)	
Fetal Macrosomia		9(10.20%)		0	
None		74(84.10%)		85(95.50%)	
Gestational age at delivery	88	39(34:41) (38.69±1.38)	89	39(32:41) (38.98±1.53)	0.034[a]
Prematurity	87		89		0.741[b]
Prematurity		7(8%)		6(6.70%)	
≥37 weeks		80(92%)		83(93.30%)	
Birth weight (gr)	88	3407.50(2300:4565)	89	3407.50(1570:4315)	0.319[a]
Length (cm)	88	51(45:56)	88	50(42:56)	0.146[a]
Head circumference (cm)	88	35(30:38) (35.15±2.27)	88	35(30:38) (34.69±1.44)	**0.029[a]**
Neonatal Hospitalization	88		73		0.126[d]
Sepsis		12(13.60%)		10/73(13.70%)	
Others		5(5.70%)		0	
None		71(80.70%)		63/73(86.30%)	

Data were presented as median (minimum: maximum), mean ± st. deviation and n%.
AMA: Adverse Maternal Age
a: Mann Whitney U Test, b: Chi-Square Test, d: Fisher-Freeman-Halton Test

Table 3. Comparison of maternal characteristics and neonatal outcomes in study group patients with and without fetal macrosomia.

	Macrosomia		
	Present (n=9)	Absent (n=79)	p-value
Age(years)	27(23:34)	29(20:42)	0.464[a]
AMA	0	15(19%)	0.348[e]
Maternal overweight	4(44.40%)	27(34.20%)	0.715[e]
Head circumference (cm)	36(35:38)	35(30:38)	0.005[a]
Infant birth weight (gr)	4290(3950:4565)	3350(2300:4085)	<0.001[a]
Infant length (cm)	52(51:55)	51(45:56)	0.001[a]
Type of Birth			0.003[d]
Vaginal Delivery	2(22.10%)	41(51.90%)	
C/S (previous pregnancy)	1(11.10%)	27(34.20%)	
C/S (primary)	6(66.70%)	11(13.90%)	

Data were presented as median (minimum: maximum) and n%.
a: Mann Whitney U Test, d: Fisher-Freeman-Halton Test, e: Fisher's Exact Test

Table 4. 100 g levels in study group patients with AMA and Overweight Pregnancies.

	50 g Pre-GDM			
	Overweight Pregnancy(n=31)	AMA≥35 (n=15)	AMA≥35 & Overweight Pregnancy (n=6)	p-value[f]
Fasting glycemia	81.20±7.63	81.27±7.19	82±4.38	0.969
1st hour	153.39±25.77	157±33.64	153.67±37.33	0.925
2nd hour	131.13±24.68	141.07±19.11	151.67±13.99	0.084
3th hour	101.16±33.56	107.27±37.81	114.50±43.87	0.006
Data were presented as mean± st. deviation f: ANOVA Test National Diabetes Data Group (NDDG) 1979 Fasting ≥ 105 mg/dL (5.8 mmol/l) 1-hour ≥ 190 mg/dL (10.6 mmol/l) 2-hour ≥ 165 mg/dL (9.2 mmol/l). 3-hour ≥ 145 mg/dL (8.0 mmol/l).				

Table-5: Independent factors affecting the increase of 50 g level

n=176	Wald	p-value	OR	95% CI	
				Lower	Upper
AMA ≥35 years	5.54	0.019	5.90	1.35	25.83
Mild Obesity	15.64	<0.001	13.38	3.70	48.37
Gravida	4.14	0.042	0.67	0.46	0.99
Week of delivery	7.39	0.007	0.63	0.45	0.88
Head circumference (cm)	6.44	0.011	1.48	1.03	1.99
Model χ^2=47.97; **p<0.001**					
Hosmer and Lemeshow Test: p=0.934					
OR: Odds ratio, CI: Confidence Interval					

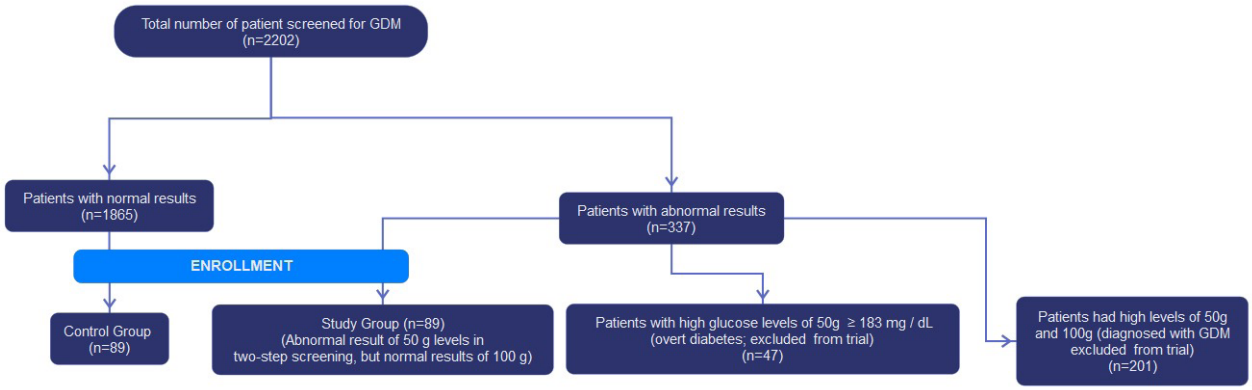

Figure 1: Flowchart of patients included in the study.

(68 kg vs. 64 kg, p=0.010). There were no differences between groups for maternal weight in the third trimester (p = 0.532) (Table-1). It was determined that the gestational weight gain (GWG) during pregnancy differed between the groups. The gestational weight gain (GWG) was lower in the study group (10 kg vs. 13kg, p<0.001) (Table-1). There was a difference between the groups in terms of the ratio of overweight pregnancy patients, and the rate of overweight pregnant women was higher in the study group (35.20% vs. 5.80%, p<0.001) (Table-1). Fasting blood glucose levels (fasting glycemia) did not differ between groups (p=0.851) (Table-1).

There was a difference between the groups according to the distribution of perinatal pathology (p=0.005) (Table-2). In the subgroup analysis, there was no difference between the groups in terms of the incidence of polyhydramnios (p>0.05) while the rate of fetal macrosomia was higher in the study group (10.20% vs. 0, p<0.05). The gestational age at delivery was lower in the study group (38.69 vs. 38.98, p=0.034) (Table-2), but the premature birth rate did not differ between the groups (p=0.741) (Table-2). There were no differences in neonatal birth weight and height (p=0.319 and p=0.146) (Table-2). It was determined that the neonatal head circumference (HC) was larger in the study group (35.15 cm vs. 34.69 cm, p=0.029) (Table-2). There were also no differences between groups for neonatal hospitalization rate (p = 0.126) (Table-2).

In total, nine macrosomic fetuses were found in the study group; there were no macrosomic fetuses in the control group (Table-2). Maternal and neonates' characteristics with and without fetal macrosomia in the study group are given in Table-3. There was no difference regarding age (27 & 29; p=0.464) and AMA (0 & 19%; p=0.348) between groups with and without fetal macrosomia. The rate of overweight pregnant patients did not differ between the groups (44.40 & 34.20, p=0.715). Birth weight, head circumference, and height measurements of neonates are different in fetuses diagnosed with prenatal macrosomia. Birth

weight (4290 g & 3350 g; p<0.001), infant height (52 cm & 51 cm; p=0.001), and median head circumference (HC) (36 cm & 35 cm; p=0.005) were higher in the fetal macrosomia group. It was determined that there was a difference in the type of birth between groups (p=0.003). In the subgroup analyses, vaginal delivery and C/S (planned) rates did not differ with or without fetal macrosomia (p>0.05), while emergent (primary) C/S rate with cephalopelvic disproportion indication was higher in the fetal macrosomia group (p<0.05).

Fasting, 1st hour, 2nd hour, and 3rd hour plasma glucose measurements of 100g levels in the abnormal GCT group (high levels of 50 g) were compared among overweight pregnant patients, AMA ≥35, and AMA ≥35 & overweight pregnant women groups (Table-4). When the table was examined: no difference was observed between the groups according to fasting, 1st hour, and 2nd hour plasma glucose measurements (p>0.05). It was determined that the 3rd hour measurement differed between the groups (p=0.006). In subgroup analyses, it was determined that the mean plasma glucose measurement of the AMA ≥35 & overweight pregnancies group at the 3rd hour was higher than the overweight pregnancies and AMA ≥35 groups (p<0.01 and p<0.05, respectively).

The present study applied multivariable logistic regression analysis to determine the risk factors affecting the 50 g level. Each variable in the study was first examined with univariate logistic regression analysis, and variables meeting the p<0.25 condition were included in the multivariable analysis. Age (≥35 years), number of gravida, abortion (presence), history of C/S (presence), first-trimester weight, type of birth, chronic disease (presence), overweight pregnancies (presence), week of delivery, infant birth weight, head circumference, and infant height measurement were included in the multivariable analysis. The analysis used the backward elimination method as the variable selection method. It was observed that the model obtained in the final step of the analysis was significant (p<0.001) and suitable for the sample data (Hosmer-Lemeshow Test: p=0.934). In the final model of multivariable analysis, it was seen that the risk of 50 g level increased in the age of 35 and above increased 5.90 [OR(95%CI): 5.90(1.35-25.83; p=0.019)] times, in overweight pregnancies, it increased 13.38 [OR(95%CI): 13.38(3.70-48.37; p<0.001)] times, and it was determined that a one-unit increase in the number of gravida decreased the 50g level by 33% [OR(95%CI): 0.67(0.46-0.99; p=0.042)]. Moreover, in the case of a one-unit increase in the newborn's head circumference measurement, the 50 g level increased by 1.48[OR(95%CI): 1.48(1.03-1.99; p=0.011)] times. On the other hand, a one-unit increase in the delivery week decreased the risk of a 50 g increase by 37% [OR(95%CI): 0.63(0.45-0.88; p=0.007)].

Discussion

The present study focuses on patients with abnormal GCT (high value of 50 g) who have not been diagnosed with GDM. In the United States, the prevalence of both pre-existing and GDM increased from 2000 to 2010 (7). We believe that the increase in the incidence of GDM and abnormal glucose levels has also increased the population of patients with high 50 g levels in the first step of double-step screening. A recent study has shown that patient whose 50g levels results between 130 and 140 mg/dl or a single-value abnormality of 100-g OGTT are at increased risk for diabetic complications (8). In our study, we selected patients with abnormal GCT results who had not been diagnosed with GDM and investigated how high levels of 50g affected the outcomes of fetuses and neonates. Moreover, we aimed to identify maternal characteristics affecting the 50 g levels of GTT, which may be a light in preventing unwanted neonatal and obstetric complications.

The proportion of women giving birth over 35 has increased over time (9, 10). A. P. Frick emphasized in his research that the AMA increased the risks of miscarriage, chromosomal abnormalities, stillbirth, fetal growth restriction, premature birth, preeclampsia, GDM, and C/S rate (11). Advanced maternal age, obesity, and a family history of diabetes are known risk factors for GDM (12). Our study also showed that the prevalence is related to maternal weight and age. When maternal overweight is added to the AMA, the risk of high blood glucose levels increases. As shown in Table 4, the group of overweight patients who were also over 35 years old had statistically higher 100 g levels at 3rd hour compared to the groups of overweight or over 35-year patients alone. This finding is important due to the fact that the studies show maternal and fetal outcomes are associated with glucose levels in pregnancy (13).

Hyperglycemia in pregnancy (HIP) is associated with a significantly increased risk of adverse events during pregnancy, intrapartum and postpartum periods. Our study showed that all nine pregnant women with fetal macrosomia were in the study group only. The median infant birth weight of macrosomic fetuses was 4290 g. Seven patients with fetal macrosomia were delivered by C/S, and six of those had C/S due to cephalopelvic disproportion (CPD) indication. These findings show that patients with high 50 g levels should be followed meticulously because this group is at a high risk of CPD. However, no difference was found between the study and control group for the type of delivery according to the C/S rate. We explained this discrepancy by selecting study group patients from normal 50 g level patients and guided the study group for diet and lifestyle changes. That is how we avoided adverse neonatal and obstetric outcomes in the study group. Kautsky-Willer A. et al. suggest that all women with GDM should receive nutritional counseling, be informed and trained in blood glucose self-monitoring, and be motivated to increase physical activity (13). The authors made these suggestions for GDM patients, but this recommendation may also be suitable for patients with high blood glucose levels of 50 g even if they are not diagnosed as GDM. In our clinic, patients with detected high glucose levels who are not subjected

to medical treatment undergo close monitoring and lifestyle modification recommendations. This is how we can also explain a weight gain that was lower in the study group than in the control group. This is how we can also explain a weight gain that was lower in the study group than in the control group.

Dabelea et al. pointed out that parity and gravidity were not significantly associated with GDM and had no effect on the GDM increase over time (14). In contrast, another study conducted by Akter S et al. shows that data on the association between reproductive events and the prevalence of diabetes mellitus are controversial but they found a relationship between multi-parity and gravidity as a risk factor for metabolic syndrome (15). Multivariate analysis results of the current study determined that a one-unit increase in gravida decreased the 50g level by 33%. The analysis also shows that in the case of a one-unit increase in the neonate's head circumference measurement, levels of 50 g increase 1.48 times. These data show that increased 50 g levels affect the neonate's head circumference (HC). Head circumference measurements were higher in the study group. Thus, patients in the study group are at risk for Cephalopelvic Disproportion (CPD), the leading cause of obstructed labor.

As we know, obstructed and prolonged labor is associated with short-term and long-term complications (16, 17). JP Neilson et al. (18) noticed that obstructed labor is an important cause of maternal deaths in communities. In another study, researchers reviewed the evolution of the human pelvis and obstructed labor (19). This article is very intriguing, but perhaps the answer is simple. As we know, obesity has risen sharply over the past three decades (20). Maternal metabolic status has also changed over recent decades, influenced by maternal excess weight and advanced age. These changes, both during pregnancy, which was shown in our study, and during the peripartum and postpartum periods, have an adverse maternal, fetal and neonatal outcome. However, obstructed labor is a preventable obstetric complication (21). So, we can prevent obstetric complications in patients with high levels of 50 g, who have not been diagnosed with GDM (study group) with attentive follow-up and timely surgery intervention.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended universal maternal hyperglycemia testing for women without a prior diagnosis of overt diabetes mellitus using a one-step 75 g oral glucose tolerance test (OGTT) (22). No recent studies of 50 g GGT have shown that how high levels in the first STEP-I of screening lead to adverse neonatal outcomes such as fetal macrosomia and increased primary C/S rate due to labor. Olagbu et al. pointed out that the 50 g GCT performed poorly compared with the 75 g OGTT for detecting hyperglycemia in pregnancy (23). The authors also emphasized that 50 gr GCT seemed as an unsuitable replacement for the 75 g OGTT. The results of our study may support the idea that the 75 g OGTT for GDM screening can identify the study population of patients and diagnose them as GDM.

Study Limitations

Since this study is retrospective, the main limitation is the lack of information on patients' diet and physical activity. Another essential limitation is the fact that the study is a single-center study with a small sample size. These limitations suggest that further research is needed to confirm the findings and better understand the underlying mechanisms of the relationships observed in this study. Future research should aim to revisit these findings in a larger, prospective study to investigate further the relationship between advanced maternal age, maternal weight, and high levels of of 50 g, in cases who have not been diagnosed with GDM. Additionally, more research is needed to explore potential interventions for reducing the risk of abnormal levels of 50 g in high-risk populations, such as increasing awareness about the importance of healthy weight management before and during pregnancy.

Conclusion

The present study aimed to investigate the risk of adverse maternal and fetal outcomes in women with abnormal 50 g but normal 100 g levels on two-step screening tests for gestational diabetes mellitus (GDM). Our results showed that the high levels of 50 g (study group) had a higher incidence of advanced maternal age and a higher proportion of overweight pregnant patients compared to the control group. Additionally, the study group had a higher rate of fetal macrosomia and larger neonatal head circumference measurements. These findings suggest that patients with high 50 g levels should be followed meticulously as this group is at high risk for cephalopelvic disproportion. However, attentive follow-up and diet and lifestyle changes in the high levels of 50 g (study group) may help to avoid adverse neonatal and obstetric outcomes. Further research is required to identify the specific maternal characteristics that affect 50 g levels and to develop interventions to prevent unwanted complications in this population.

Ethics Committee Approval: The study was approved by the Local Clinical Research Ethics Committee (Approval number: 2020-9/8).

Data Sharing Statement: The raw data supporting the conclusions of this article will be made available without reservation by the authors upon request.

Conflict of Interest: No conflict of interest was declared by the authors.

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Author contributions:

SRO: Research concept and design, collection and/or assembly of data, writing the article, critical revision of the article, final approval of the article

BAD: Research concept and design, critical revision of

the article, final approval of the article

ZA: Research concept and design, data collection, critical revision of the article, final approval of the article

OOU: Collection and/or assembly of data, critical revision of the article, final approval of the article

GO: Research concept and design, data analysis and interpretation, final approval of the article

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ORIGINAL ARTICLE

Determination of University Students' Preventive Attitudes for Lung Cancer and Healthy Life Awareness and The Influencing Factors

Üniversite Öğrencilerinin Akciğer Kanserinden Korunmaya Yönelik Tutum ve Sağlıklı Yaşam Farkındalıkları ile Etkileyen Faktörlerin Belirlenmesi

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ABSTRACT

Objective: This study was conducted to determine the attitudes of university students towards lung cancer screening and healthy lifestyle and the factors affecting these attitudes.
Material and Method: In this descriptive cross-sectional study, data were collected from 295 students between September 2022 and February 2023 using personal information form, Healthy Living Awareness Scale, and Health Belief Model Scale for Lung Cancer and Screenings.
Results: It was observed that the perception of sensitivity and perception of obstacle subscales of the Health Belief Model Scale for Lung Cancer and Screenings were higher in males than females, and those with extended families had higher perception of violence and perception of obstacle than those with nuclear families. Perception of sensitivity and perception of violence decreased as general health status improved. Sensitivity perception was higher in smokers compared to non-smokers. Health motivation was higher in non-smokers than smokers. In addition, perception of barrier was higher in alcohol consumers compared to non-consumers. As the awareness of healthy living increased, the perception of violence and perception of barrier subscales of the health belief model of lung cancer orientation decreased.
Conclusion: Consequently, it was determined that the students perceived lung cancer screening as beneficial, but they were not sensitive enough to have screening. The barrier perception related to screening was low, the health motivation was high and the severity perception was moderate.

Keywords: Lung Cancer Awareness, Healthy Life Awareness, University Students, Health belief model

ÖZ

Amaç: Bu çalışma, üniversite öğrencilerinin akciğer kanseri taramalarına ve sağlıklı yaşam tarzına yönelik tutumlarını ve bu tutumları etkileyen faktörleri belirlemek amacıyla yapılmıştır.
Gereç ve Yöntem: Tanımlayıcı-Kesitsel nitelikteki bu çalışmada veriler Eylül 2022-Şubat 2023 tarihleri arasında 295 öğrenciden kişisel bilgi formu, Sağlıklı Yaşam Farkındalık Ölçeği, Akciğer Kanseri ve Taramalarına Yönelik Sağlık İnanç Modeli Ölçeği kullanılarak toplanmıştır.
Bulgular: Akciğer Kanseri ve Taramalarına Yönelik Sağlık İnanç Modeli Ölçeği duyarlılık algısı ve engel algısı alt ölçeklerinin erkeklerde kadınlara göre daha yüksek olduğu ve geniş aileye sahip olanların çekirdek aileye sahip olanlara göre daha yüksek şiddet algısı ve engel algısına sahip olduğu görülmüştür. Genel sağlık durumu iyileştikçe duyarlılık algısı ve şiddet algısı azalmıştır. Sigara içenlerde duyarlılık algısı içmeyenlere göre daha yüksektir. Sigara içmeyenlerin sağlık motivasyonu sigara içenlere göre daha yüksekti. Ayrıca, alkol tüketenlerde tüketmeyenlere kıyasla engel algısı daha yüksekti. Sağlıklı yaşam farkındalığı arttıkça Akciğer kanserine yönelim sağlık inanç modelinin şiddet algısı ve engel algısı alt ölçeklerinin azaldığı görülmüştür.
Sonuç: Öğrencilerin akciğer kanseri taramasını faydalı olarak algıladıkları, ancak tarama yaptırmak için yeterince duyarlı olmadıkları belirlenmiştir. Taramaya ilişkin engel algısı düşük, sağlık motivasyonu yüksek ve şiddet algısı orta düzeydedir.

Anahtar Kelimeler: Akciğer Kanseri Farkındalığı, Sağlıklı Yaşam Farkındalığı, Üniversite Öğrencileri, Sağlık inanç modeli

Introduction

Lung cancer is one of the most common cancers and the leading cause of death worldwide (1,2). The incidence of lung cancer in Ireland is 1,407 in men and 1,157 in women. The mortality rate is 1,069 per year in men and 785 per year in women (3). In the UK, the5-year relative survival rate for early-stage lung cancer is 57%, but it is only 3% for patients diagnosed in advanced stage (4). In USA, the estimated incidence of lung cancer in 2023 is 12.2% for all cancers and mortality is 20.8% for all cancers; the 5-year survival rate between 2013 and 2019 is 25.4 (5). In Turkiye, lung cancer is seen in 55.6% of men and 10.9% of women (6). On average, 18% of lung cancer patients survive for five years (7). Fifty-seven percent of patients are diagnosed at a late stage, resulting in a higher mortality rate (2). One study reported that annual low-dose computed tomography (CT) scans for early diagnosis of lung cancer reduced mortality by 20% (8). Increased awareness of symptoms has been reported to increase the number of people with persistent coughs who seek primary health care and have a chest x-ray, leading to more lung cancer diagnoses (9,10). In another study, it was reported that 2.9% of high-risk smokers underwent lung CT scanning in 2011 and this rate increased to 5.8%

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in 2015 (11). In other studies, the increase in the rate of lung CT scanning in high-risk smokers is estimated to be 1.9% (12,13). Therefore, early detection of signs and symptoms of lung cancer and increased public awareness are crucial to reduce cancer incidence and mortality in low- and middle-income countries (14).

Similar or lower levels of awareness of lung cancer risks and symptoms have been observed in the UK (15) and Canada (16). Studies have reported that public awareness of cancer symptoms has a positive effect on early detection rates of lung cancer (17,18). In order to prevent cancer, WHO has implemented action plans against the main preventable risk factors of cancer and recommended the implementation of early diagnosis and screening programs. With this action plan, it is predicted that new cancer cases, cancer cases diagnosed at advanced stages and deaths due to breast, cervical and colorectal cancers will decrease (19).

For lung cancer, which increases with age, it may be important to start screening at an early age. In the light of this information, this study was conducted to determine the awareness of university students representing the young population about lung cancer screening and healthy living and the factors affecting them.

Materials and Methods

Type of the Study and Sampling

This descriptive cross-sectional study was conducted to determine the awareness of university students about lung cancer screening and healthy living and the factors affecting them. A total of 295 undergraduate and associate degree students from a state university were included in the sample. The inclusion criteria were being a student of that university and agreeing to participate in the study. In the study, the data were collected from the students who agreed to participate in the study.

Data Collection Tools

In the study, the data were collected between September 2022 and February 2023 using a personal information form, the Healthy Life Awareness Scale (HLAS) and Health Belief Model Scale for Lung Cancer and Screening (HBMSLCS). The data were collected with a questionnaire form created through the google form.

Personal Information Form: It is a questionnaire that was prepared by the researchers in accordance with the literature and includes questions about characteristics of the participants such as age, gender, and income level.

Healthy Life Awareness Scale (HLAS): This scale was developed by Özer and Yılmaz in 2020 and it consists of 15 items and four subscales. The change subscale consists of five items, the socialization subscale consists of three items, the responsibility subscale consists of three items and the nutrition subscale consists of three items. The minimum score that can be obtained from this scale is 15 and the maximum score is 75. A high score indicates a high awareness of healthy living. The Cronbach's alpha value was 0.813 (20). In this study, the Cronbach's alpha value of the scale was 0.972.

Health Belief Model Scale for Lung Cancer and Screening (HBMSLCS): This scale was developed by Demir Dogan and colleagues in 2021 and it consists of 30 items; the HBMSLCS consists of five subscales (perceived trust and benefits, perceived sensitivity, perceived barriers, perceived health motivation and perceived motivation). Items are scored on a 1 to 5 point scale (1-strongly disagree, 2disagree, 3-undecided, 4-agree, and 5-strongly agree). The minimum and maximum scores on this scale range from 10 to 50 for trust and perceived benefits, 5 to 25 for perceived susceptibility, 4 to 20 for perceived barriers, 6 to 30 for perceived health motivation, and 5 to 25 for perceived seriousness. Higher scores denote greater sensitivity and caring, perceived benefits and perceived barriers in perceived barriers. The Cronbach alpha value of the trust-benefit perception sub-dimension was 0.779, the Cronbach alpha value of the sensitivity perception sub-dimension was 0.833, the Cronbach alpha value of the barrier perception sub-dimension was 0.737, and the Cronbach alpha value of the sub-dimension of the perception of health motivation was 0.725. (21). In the present study, the perceived trust and benefit subscale was 0.864, the perceived sensitivity subscale was 0.914, the perceived barriers subscale was 0.840, the perceived health motivation subscale was 0.800, and the perceived seriousness subscale was 0.778.

Statistical Analysis

Descriptive methods (mean, standard deviation, median, frequency and percentage) were applied to analyze the data. Mann-Whitney U-test, t-test, Pearson correlation analysis and Spearman correlation analysis were used to analyze the data.The results were expressed as 95% confidence interval and significance level as $p<0.05$.

Ethical Considerations

Ethics committee approval was obtained from Gümüşhane University Scientific Research and Publication Ethics Committee (dated 27/04/2022 and numbered 2022/3) in order to conduct the study. Participants verbal informed consent was obtained. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

The mean age of the students was 22.08±5.56, and 69.2% of them were female. Majority of the students (92.9%) were single and 48.5% were the first-year students. While the rate of those who expressed their income as 'income equal to expenses' was 57.6%, 79% had a nuclear family type and 71.9% resided in a dormitory. It was determined that a great majority of the group did not have any chronic disease (92.2%), did not drink alcohol (95.9%), did not smoke (79.3%), and 56.9% defined their general health as good. A great majority of the students did not have a cancer patient in their first-degree relatives (85.1%) (Table 1).

Table 1: Socio-demographic characteristics (n=295)

	n	%
Gender		
Female	204	69,2
Male	91	30,8
Marital status		
Married	21	7,1
Single	274	92,9
Family type		
Nuclear family	233	79,0
Extended family	62	21,0
Grade		
1	143	48,5
2	67	22,7
3	32	10,8
4	53	18,0
Income status		
Income less than expenses	96	32,5
Income equals expense	170	57,6
Income more than expenses	29	9,8
Current residency		
With family	60	20,3
in the dormitory	212	71,9
At home with friends	16	5,4
alone at home	7	2,4
General health Status		
bad level	7	2,4
Medium-level	107	36,3
good level	168	56,9
Having any chronic disease		
Yes	23	7,8
No	272	92,2
Smoking status		
Yes	61	20,7
No	234	79,3
Alcohol intake		
Yes	12	4,1
No	283	95,9
Family cancer history		
Yes	44	14,9
No	251	85,1

As a result of the statistical analysis, it was determined that there was a positive significant correlation between general health status and income status. The participants' general health improved as their income level increased (p=0.001) (Table 3).

Total mean scores of the subscales of the HBMSLCS were 43.56±4.98 for the trust-benefit perception subscale, 11.81±5.75 for the sensitivity perception subscale, 10.13±4.60 for the barrier perception subscale, 21.48±3.91 for the health motivation subscale, and 17.49±4.57 for the severity perception subscale.

As a result of the statistical analysis, it was determined that there was a significant difference between gender and the sensitivity perception and barrier perception subscales of the HBMSLCS. Male participants' sensitivity perception (p=0.009) and barrier perception were higher compared to their female counterparts (p=0.001). The severity perception was higher in those with chronic disease than those without chronic disease (p=0.004). There was a significant correlation between family type and the barrier and severity perception. The barrier perception was higher in those with extended families than those with nuclear families (p=0.014). Those with extended families had a higher severity perception than those with nuclear families (p=0.005) (Table 2).

It was determined that the sensitivity perception was higher in smokers than non-smokers (p=0.033). Non-smokers had higher health motivation than their smoker counterparts (p<0.001). In addition, alcohol consumers had a higher barrier perception than those who did not consume alcohol (p=0.014) (Table 2).

As a result of the statistical analysis, it was determined that there was a negative significant correlation between the general health status and the sensitivity perception and severity perception. As the general health status improved, the sensitivity perception (p=0.009) and the severity perception (p=0.013) decreased (Table 3).

The total mean score of the HLAS was 49.41±17.33. Total mean scores of its subscales were 17.39±6.71 for the change subscale, 12.92±4.72 for the socialization subscale, 10.14±3.86 for the responsibility subscale, and 8.94±3.58 for the nutrition subscale.

As a result of the statistical analysis, it was found that there was a negative significant correlation between the total mean score of the HLAS and the barier perception and the severity perception of the HBMSLCS. It was observed that the barrier perception (p<0.001) and the severity perception (p=0.014) decreased as the healthy life awareness increased. In addition, as the university years increased, the healthy life awareness increased, as well (p<0.001) (Table 3).

It was found that there was a negative significant correlation between the change subscale mean score of the healthy life awareness scale and the sensitivity perception, barrier perception, severity perception and health motivation subscales of HBMSLCS. As change subscale mean score increased, the sensitivity perception (p=0.020), the barrier perception (p<0.001), the severity perception (p=0.021) and the health motivation (p=0.017) decreased. In addition, the change subscale mean score increased as the university years increased (p<0.001) (Table 3).

It was determined that as the mean score of the socialization subscale of the HLAS increased, the barrier perception decreased (p<0.001). The socialization

Table 2: Variables Affecting the Dimensions of the Health Belief Model Scale for Prevention from Lung Cancer

		Gender		Presence Of Chronic Disease		Family Type		Cigarette Use		Alcohol Use	
		Female	Male	Yes	No	Nuclear Family	Extended Family	Yes	No	Yes	No
Trust-Benefit Perception	Mean ±sd	43,73±4,35	43,19±6,18	43,52±3,17	43,57±5,11	43,63±4,85	43,32±5,50	43,85±4,79	43,49±5,04	42,16±5,85	43,62±4,95
	p	0,393*		0,962*		0,662*		0,620*		0,321*	
Sensitivity Perception	Mean ±sd	11,13±5,30	13,34±6,43	12,91±5,54	11,72±5,77	11,38±5,37	13,43±6,79	13,21±5,10	11,44±5,86	14,91±6,06	11,68±5,71
	p	0,009**		0,341*		0,069**		0,033*		0,056*	
Barrier Perception	Mean ±sd	9,52±4,30	11,51±4,96	10,34±4,44	10,12±4,62	9,75±4,42	11,56±5,01	10,13±4,41	10,14±4,66	13,33±4,09	10,00±4,58
	p	0,001**		0,821*		0,014**		0,988*		0,014*	
Health Motivation Perception	Mean ±sd	21,25±3,81	22,00±4,12	21,08±4,18	21,51±3,90	21,43±3,80	21,64±4,34	19,73±4,29	21,93±3,69	22,16±5,00	21,45±3,87
	p	0,129*		0,616*		0,712*		<0,001*		0,537*	
Motivation Perception	Mean ±sd	17,36±4,71	17,78±4,26	20,08±3,47	17,27±4,59	17,14±4,54	18,79±4,52	17,54±4,18	17,47±4,68	17,66±4,47	17,48±4,59
	p	0,470*		0,004*		0,005**		0,925*		0,893*	

* t testi, **Mann-Whitney U

Table 3: Correlation between the Dimensions of the Health Belief Model Scale for Prevention from Lung Cancer, the Healthy Life Awareness Scale and its sub-dimensions, and some variables

	Trust-Benefit Perception		Sensitivity Perception		Barrier Perception		Health Motivation Perception		Motivation Perception		Income Status		Students grade	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
HLAS Total	0,032	0,588*	-0,113	0,054*	-0,267	<0,001*	-0,094	0,109*	-0,143	0,014*	0,014	0,810**	0,245	<0,001**
HLAS Change	0,007	0,910*	-0,136	0,020*	-0,261	<0,001*	-0,139	0,017*	-0,135	0,021*	-0,006	0,925**	0,259	<0,001**
HLAS Socialization	0,068	0,246*	-0,079	0,174*	-0,227	<0,001*	-0,043	0,462*	-0,043	0,462*	0,037	0,527**	0,213	<0,001**
HLAS Responsibility	0,053	0,366*	-0,105	0,072*	-0,272	<0,001*	-0,078	0,184*	-0,124	0,034*	0,003	0,961**	0,232	<0,001**
HLAS Nutrition	-0,124	0,034*	-0,071	0,222*	-0,205	<0,001*	-0,051	0,384*	-0,141	0,016*	0,026	0,659**	0,166	0,004**
General Health Status	-0,024	0,680**	-0,151	0,009**	-0,103	0,076**	0,040	0,494**	-0,144	0,013**	0,197	0,001**	0,035	0,549**

*Pearson Correlation, ** Spearman's Correlation

subscale mean score also increased as the university years increased (p<0.001). It was found that there was a negative significant correlation between the mean score of the responsibility subscale of the HLAS and the barrier perception and the severity perception. As the mean score of the socialization subscale increased, the barrier perception (p<0.001) and the severity perception (p=0.013) decreased. The mean score of the responsibility subscale (p<0.001) and the nutrition subscale (p=0.004) also increased as the university years increased (Table 3).

It was found that there was a negative significant correlation between the nutrition subscale mean score of the HLAS and the trust-benefit perception, the barrier perception and the severity perception in the HBMSLCS. As the nutrition subscale mean score increased, the trust-benefit perception (p=0.034), the barrier perception (p<0.001) and the severity perception (p=0.016) decreased (Table 3).

Discussion

In this study, which was conducted to determine university students' awareness of lung cancer screening, it was found that the perception of trust-benefit of the lung cancer belief model was high, so the screening was perceived as beneficial. It was determined that the total mean score of the sensitivity perception subscale was low, so there was not enough sensitivity about screening. The total mean score of the barrier perception subscale was low, so the barrier perception related to screening was low. The health motivation was high and the severity perception was moderate. A study conducted in Estonia reported a moderate level of awareness of lung cancer risks and symptoms (22). It was observed that level of awareness of lung cancer risks and symptoms is similar between or lower in England (15) or Canada (16). In other studies, it was determined that the level of knowledge about lung cancer symptoms was insufficient (15,23,24). Studies have shown the positive effect of raising public awareness about cancer symptoms on the early detection rates of lung cancer (17,18). No previous study of the sample group of our study was found. However, when we look at the studies conducted with lung cancer symptom awareness, it is thought that the results are similar.

In the present study, it was determined that sensitivity and barrier perception of the lung cancer belief model were higher in men than in women. Those with extended families had higher barrier and severity perceptions than those with nuclear families. The sensitivity perception and the severity perception decreased as the general health status improved. An Australian study reported that women were better

aware of lung cancer symptoms (25). Likewise, a study reported that women were better aware of lung cancer symptoms (26). In another study, it was stated that lung cancer awareness of women and men was similar (27). The differences in the results of the study may be attributed to the differences in the sample groups.

In the present study, it was determined that the sensitivity perception was higher in smokers compared to their non-smoker counterparts. Non-smokers had higher health motivation than smokers. Moreover, the barrier perception was higher in alcohol cunsumers compared to those who did not consume alcohol. In a study, it was found that most of the smokers did not have lung cancer screening, and although the screening rates increased, this rate did not increase among smokers (28). Another study revealed that most of high-risk smokers have never heard of or had screening for lung cancer, nor were they aware of the existence of a screening test for lung cancer (29). Studies on attitudes towards lung cancer screening have shown that smokers place less value on the benefits of lung cancer screening. It has also been reported that stigma is a barrier to participation in screening (30,31). Furthermore, emotional barriers such as fear of being diagnosed with lung cancer (32) and the belief that the lungs are an incurable organ (31,33) have been reported to reduce participation in lung cancer screenings.

It was observed that as the healthy life awareness increased, the barrier perception and severity perception subscales of the lung cancer belief model decreased. As the awareness of change, which is the subscale of the healthy life awareness scale, increased, the subscales of the lung cancer awareness scale, the barrier perception, seriousness perception, and health motivation subscales of the lung cancer belief model decreased. As the mean score of the socialization subscale of the healthy life awareness scale increased, the barrier perception and seriousness perception subscales of the lung cancer belief model decreased. Likewise, as the mean score of the nutrition subscale of the healthy living awareness scale increased, the trust-benefit perception, barrier perception, and seriousness perception subscales of the lung cancer belief model decreased. In a study, it was determined that as the healthy life awareness increased, the positive attitude towards cancer screening increased. Similarly, it has been reported that as the awareness of change, socialization, responsibility, and nutrition subscales of Healthy Life Awareness Scale increase, the positive attitude towards cancer screening increases (34). Similarly, in another study, a significant difference was reported between breast self-examination and health perception score (34). In the light of these results, it can be asserted that high healthy life awareness has a positive effect on lung cancer awareness.

Conclusion

• The results showed that students perceived lung cancer screening as beneficial, but were not sufficiently sensitized to be screened.

• Perceptions of barriers to screening were low, health motivation was high, and perceptions of severity were moderate.

• Perceptions of susceptibility and barriers to lung cancer are higher in men than in women, and perceptions of susceptibility and severity decrease as general health status improves.

• As healthy lifestyle awareness increased, perceptions of barriers and severity towards lung cancer screening decreased.

• It is recommended that studies with larger sampless hould be conducted to increase lung cancer awareness and lung cancer awareness campaigns should be emphasized.

Limitations

The results obtained from the research are limited to the students studying at Gümüşhane University.

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Ethical Aspects of the Study/Ethics Committee Approval:

Ethics committee approval was obtained from Gümüşhane University Scientific Research and Publication Ethics Committee (dated 27/04/2022 and numbered 2022/3) in order to conduct the study. Participants verbal informed consent was obtained. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of interest:

The authors have no vested interest.

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ORIGINAL ARTICLE

Indoor Air Quality of a Medical Faculty Hospital and Its Effect on Those in the Environment

Bir Tıp Fakültesi Hastanesi İç Ortam Hava Kalitesi ve Ortamda Bulunanlara Etkisi

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ABSTRACT

Aim: The purpose of the current study is to measure indoor air quality parameters in a medical faculty hospital and to determine the medical complaints of hospital staff and patients/patient relatives regarding indoor air quality.
Methods: This cross-sectional, descriptive research was conducted with 442 participants between February 28 and March 22, 2021. For the indoor air quality in the hospital; temperature, relative humidity, air flow rate, light level, nitrogen oxide (NO), hydrogen sulfide (H2S), sulfur dioxide (SO2), carbon monoxide (CO), carbon dioxide (CO2) gas levels were evaluated according to the standards.
Results: It was determined that 80.3% of the air temperature and 22.7% of the relative humidity measurements in the study were in the standard limits and almost all of the air flow velocity and 81.0% of the illumination level measurements were not in standard limits. It was determined that particulate matter level was at normal levels according to International Organization for Standardization (ISO) 5 class in the all-environmental area. NO, H2S and SO2 were detected in the hospital with indoor gas measurements. CO gas was detected in a small part of the hospital. The majority of CO2 measurements were in line with standards. The most common symptoms of the participants associated with indoor air of the hospital were fatigue and dyspnea.
Conclusion: It was determined that some of the indoor air quality parameters did not comply with the standards and the participants had health complaints related to this. Indoor air quality parameters should be measured at regular intervals and necessary arrangements should be made to comply with the standards.

Keywords: Indoor air quality, Hospital, Health, Medical symptom

ÖZ

Amaç: Bu çalışmada bir tıp fakültesi hastanesinde iç ortam hava kalitesi parametrelerini ölçmek, hastane personelinin ve hasta/hasta yakınlarının iç ortam hava kalitesine ilişkin tıbbi semptomlarını belirlemek amaçlanmıştır.
Yöntem: Kesitsel tipteki bu araştırma 28 Şubat – 22 Mart 2021 tarihleri arasında, 442 katılımcıyla gerçekleştirilmiştir. Hastane iç ortam hava kalitesi için sıcaklık, bağıl nem, hava akım hızı, aydınlık düzeyi, nitrojen oksit (NO), hidrojen sülfür (H2S), sülfür dioksit (SO2), karbon monoksit (CO), karbon dioksit (CO2) gaz ölçümleri yapılarak standartlara göre değerlendirilmiştir.
Bulgular: Çalışmada ölçülen hava sıcaklığı ölçümlerinin %80,3'ünün, bağıl nem ölçümlerinin % 22,7'si standartlara uygun olduğu belirlendi. Ölçümlerin neredeyse tümünde hava akımı hızının standartlara uygun olmadığı belirlendi. Aydınlatma düzeyi ölçümlerinin %81,0'ının standartlara uygun olmadığı belirlendi. İç ortam partiküler madde düzeyi ölçümü ile tüm ortamların ISO 5 sınıfına ait olduğu tespit edildi. İç ortam gaz ölçümleri sonucu hastanede NO, H2S, SO2 gazlarına rastlanmadı. CO gazı hastanenin küçük bir kısmında tespit edildi. CO2 ölçümlerinin neredeyse tamamı standartlara uygundu. Katılımcıların hastanenin iç ortam havasıyla ilgili en sık görülen semptomları yorgunluk ve nefes darlığıydı.
Sonuç: İç ortam hava kalitesi parametrelerinden bir kısmının standartlara uymadığı ve buna bağlı katılımcıların sağlık yakınmaları belirlenmiştir. İç ortam hava kalitesi parametreleri düzenli aralıklarla ölçülmeli ve standartlara uygun olması için gerekli düzenlemeler yapılmalıdır.

Anahtar Kelimeler: İç hava kalitesi, hastane, insan sağlığı, semptom

Introduction

Indoor air pollution is defined as the presence of chemical, biological and physical factors that may harm human health in the indoor air of buildings (1). Indoor air quality contains lighting, ergonomics, acoustics and temperature factors in addition to pollutants such as carbon monoxide (CO), carbon dioxide (CO2) (2). Indoor temperature is the major parameter of thermal comfort. According to the American Society of Heating, Cooling and Air Conditioning Engineers (ASHRAE) standards, the temperature is expected to be 20-25.5 °C for ideal conditions. The relative humidity indoors should be in the range of 30-60%. In the absence of humidity in the air, breathing becomes difficult, infectious diseases, stress and fatigue may occur (3-5). Insufficient lighting causes accidents and decrease in work efficiency. The minimum illumination level in the working environment is accepted as 500 lux (6). The main sources of CO in indoor air are fireplaces, stoves, exhaust fumes from vehicles and cigarette smoke (7). The parameter that

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directly shows how intensively an environment is used by people is the CO2 concentration. Ambient air with a CO2 content of less than 1000 ppm is defined as 'acceptable indoor air quality' (8). Exposure to Hydrogen Sulfide (H2S) may cause eye and upper respiratory tract irritation (9). Due to exposure to sulfur dioxide (SO2), stenosis in the airways, wheezing and dyspnea occur (10). Nitrogen Oxide (NO) may cause eye irritation, exacerbation of asthma, and chronic respiratory diseases (11). Complex mixtures of inorganic and organic substances in the atmosphere are defined as particulate matter (PM) (12). The standard considered in terms of particulate matter is "ISO 14644-1:1999(E) Clean rooms and related controlled environments-Part 1: Classification of air cleanliness" (13).

The primary aim of the current descriptive study is to evaluate the physical factors (temperature, relative humidity, airflow rate, etc.) and indoor air quality in the hospital. The second is the comparison of these data with standard parameters. The third purpose is to reveal the environmental-related medical symptoms of the hospital staff and the patient/patient relatives in the hospital.

Methods

This cross-sectional descriptive study was conducted between February 28 and March 22, 2021. The sample size for the number of participants to be surveyed was calculated as a total of 435 using the "G-power" program, with 95% confidence interval, 85% power, 5% margin of error, 50% unknown prevalence rate and ½ the ratio of the groups.

Approval from Necmettin Erbakan University Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 19/02/2021, Number: 2021/3120), written permission from Medical Faculty Hospital Chief Physician, and informed consent form from the participants were obtained for the study. The research was funded by the Necmettin Erbakan University Scientific Research Projects Coordinatorship (Project No: 201518007).

The campus of university has 2 different hospitals. The new campus consists of a monoblock building with a capacity of 900 beds. The old campus consists of a total of 7 separate blocks of buildings and the deanery building. The hospital on the new campus uses central air-conditioning and ventilation systems, and there are large opening windows throughout the building. While one block of the buildings in the old campus (the oncology building) has central ventilation and air conditioning, the other buildings do not have central ventilation systems. All buildings in the old campus had operable windows. In this study, all measurements and evaluations were carried out in two different hospitals (old hospital campus; new hospital campus). Extech RH300 brand was utilized for temperature and humidity measurement; TSI 9515 brand portable anemometer for air flow velocity measurement, Extech EA31 brand for illumination level measurement, Cem DT-9880 brand for particulate matter measurement with dimensions of 0,3 µm, 0,5 µm, 1,0 µm, 2,5 µm, 5,0 µm, 10,0 µm, and Honeywell Multirae Lite brand for gas measurements. All measurements were carried out momentarily, at least 1 meter above the ground at the midpoint of the field, and at two different times; in the morning and in the afternoon.

The survey for hospital staff and patients/patient relatives, which was prepared by reviewing the current literature, consists of 27 items. It asks about socio-demographic characteristics, health status characteristics and symptoms related to indoor air quality (14-16). Questions to assess opinions and symptoms related to indoor air quality are listed in Table 2 and Table 3.

SPSS (Statistical Package for Social Sciences) 27.0 program was used for data analysis. Frequency data were given using numbers (n) and percent (%), numerical data using mean±standard deviation (sd), median (1st-3rd quartile). Chi-square ($\chi 2$) test was used to compare categorical data. Compliance of numerical data with normal distribution was examined by Kolmogorov-Smirnov and Shapiro Wilk tests. Student t and One-Way ANOVA tests were employed to compare normally distributed numerical data. Tukey test was utilized for post hoc analysis of ANOVA test. Mann Whitney U and Kruskall-Wallis post hoc Dunn-Bonferroni tests were used for non-normally distributed numerical variables. In new and old hospital campuses, data according to departments were evaluated using two-way ANOVA test. Statistical significance level was accepted as $p<0.05$.

Results

In this research, 132 measurements were conducted in 40 different sections. 63.6% of the measured areas were in the new hospital campus and 36.4% were in the old hospital campus. The measurement areas were comprised of polyclinics 27.3%, inpatient clinics 24.2%, laboratories 12.1%, technical-support units 12.1%, administrative units 10.6%, social areas 9.1% and 4.6% operating rooms.

The mean temperature measurement value in all sections included in the research was determined as 22.81±2.03 °C. Comparison of temperature measurements conducted in hospital indoor environments according to departments was statistically significantly different (p=0.001). Temperature values measured in inpatient clinics were statistically higher than the values measured in outpatient clinics, social areas, technical-support units and administrative units (p values, respectively; p=0.001, p=0.001, p=0.001, p=0.007). The temperature values measured in social areas were statistically significantly lower than the values measured in outpatient clinics, inpatient clinics, laboratories and operating rooms (p values, respectively; p=0.027, p=0.001, p=0.024, p=0.029). Temperature values measured in hospital units were statistically significantly different in comparison to hospital campus (p=0.001, Figure 1A).

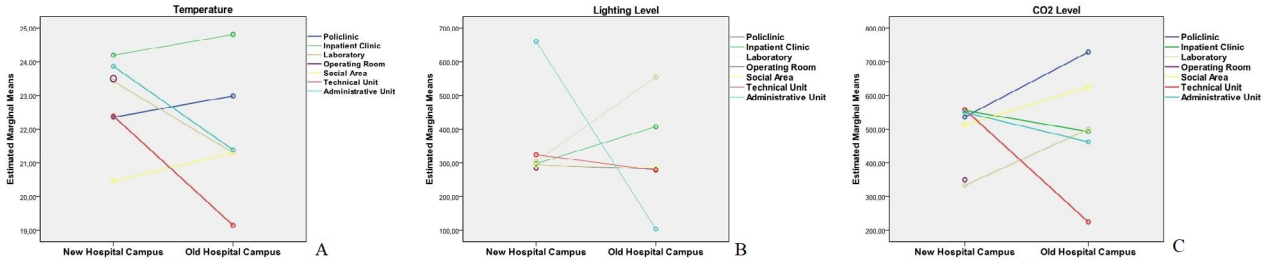

Figure 1. Temperature values (A), lighting (B) and carbon dioxide (CO2) (C) levels in the units of university hospital (old campus and new campus)

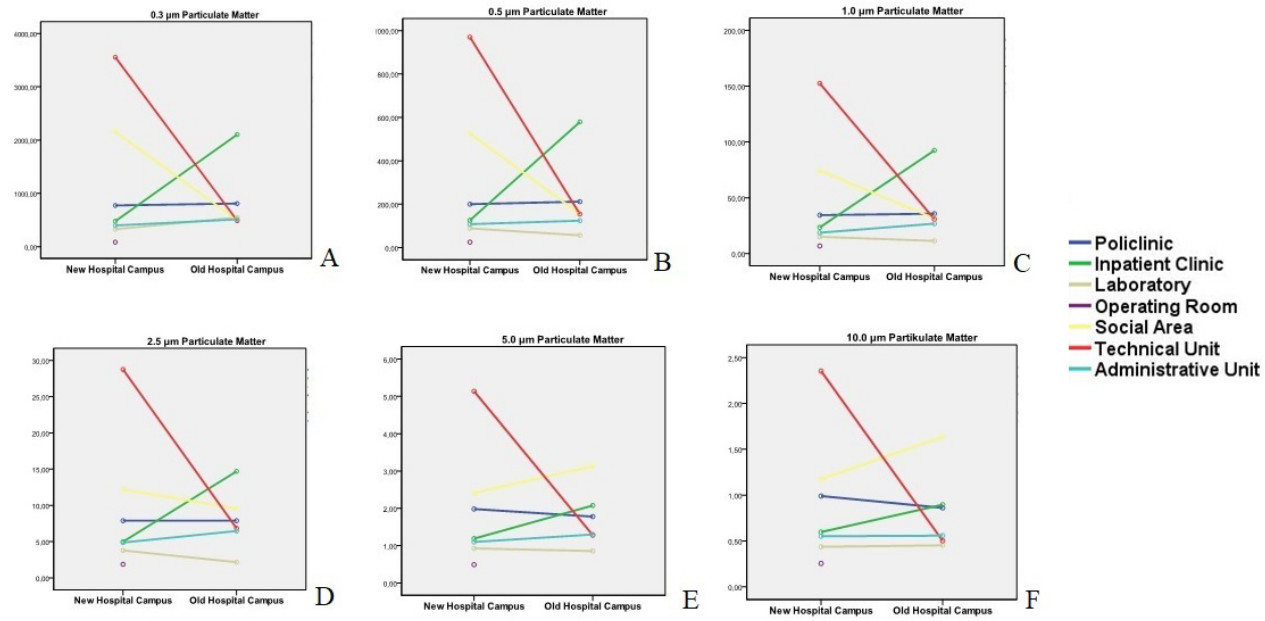

Figure 2. Levels of particulate matter (A: 0.3µm, B: 0.5 µm, C: 1.0 µm, D: 2.5 µm, E: 5.0 µm, F: 10.0 µm) in the units of university hospital according to diameters (old campus and new campus)

80.3% of all temperature measurements in the research were found acceptable in terms of the standards. The temperature measurements were evaluated according to the standards, and 15 measurements were lower than 20.0 °C and 11 measurements were higher than 25.5 °C. The compliance of the temperature measurements of the hospital units with the standards was statistically significantly different (p=0.004). This difference was due to the fact that the temperature measurements recorded in the polyclinic complied with the standards at a higher rate than in the other units.

The median of the relative humidity measurement value in the research was determined as 20.85% (16.62-29.00). Humidity measurements were compared according to the sections and there was statistically significant difference (p=0.003). The reason for this difference is that the humidity measurements conducted in the operating room were lower than the outpatient clinics, inpatient clinics, social areas, technical units and administrative units (p values are respectively; p=0.005, p=0.010, p=0.005, p=0.005, p=0.001). Laboratory measurements were lower in the outpatient and inpatient clinics (p values; p=0.035, p=0.020, respectively). Indoor relative humidity measurements in the new campus of the hospital were statistically significantly lower than the measurements in the old hospital campus (p=0.001). Statistically significant difference was not detected between the humidity values in the hospital units examined according to the hospital campus.

When the relative humidity measurements were evaluated according to the standards, a total of 102 measurements (77.2%) with a humidity level of less than 30% were detected while humidity measurements above 60% were not detected. It was determined that the relative humidity measurement in accordance with the standards was not recorded in the new hospital campus. The measurements in the new hospital campus were found lower than the standards at a higher rate when compared to the old hospital campus (p=0.001). Statistical difference was not found when the humidity measurement rates, which are in accordance with the standards and which are not in accordance with the standards, were compared according to the hospital units.

The median of the airflow measurement value in the hospital departments was determined as 10.0 (0.0-10.0) mm/sec. When airflow velocity measurements were compared according to the sections, statistically significant difference was not found. It was determined that the air flow velocity measurements in the old campus were lower than the air flow velocity measurements in the new campus (p=0.028). There was not statistical difference in the air flow velocity values in the hospital units according to the hospital campus.

When the airflow velocity values were compared according to the standards, the airflow velocity, which was in the range of 100-500 mm/sec, was determined in two measurements; one of the outpatient clinic measurements and one of the inpatient clinical measurements. 98.4% of all measurements conducted were not compatible with the standards. Both measurements within the standards were recorded in the old hospital campus.

The median of the indoor lighting level value was determined as 262.50 (152.00-431.50) lux. There was not statistically significant difference between the measurements of the illumination level according to the hospital departments. A statistically significant difference was determined in the lighting level values measured in the hospital units in comparison to the hospital campus (p=0.001). The illumination levels measured in the outpatient clinic, social area, technical-support unit and administrative units were higher in the new hospital campus, and the values measured in the inpatient clinics and laboratories were higher in the old hospital campus (Figure 1B).

When the illumination level values were compared according to the standards, 25 measurements were determined that they complied with the standards (>500 lux). 81.0% of the measurements were not compatible with the standards. Statistical difference was not found in the comparison of the appropriate and inappropriate lighting level measurements according to the hospital campus and hospital departments.

Particulate matter level measurements performed in the hospital are presented in Table 1. Measurements of all particulate matter dimensions were detected at similar levels in the old and new hospital campus. A statistically significant difference was found in measurements of all particulate matter dimensions according to hospital departments (p=0.001). When the particulate matter measurements in the indoor environment included in the research were evaluated according to the standards, it was observed that all measurements belonged to the ISO-5 class.

A statistically significant difference was detected in all particulate matter levels measured in hospital units compared to hospital campus (p=0.001). All particulate matter levels measured in technical-support units and outpatient clinics were detected higher in the new hospital campus, and all particulate matter levels measured in inpatient clinics were higher in the old campus. The 5.0 µm particulate matter levels measured in the social areas were higher in the old hospital campus, and the other particulate matter levels were higher in the new hospital campus. The level of 0.3 µm particulate matter measured in the laboratories was higher in the old hospital campus, and the other particulate matter levels were higher in the new hospital campus. Particulate matter levels measured in administrative units were similar in general in two campuses (Figure 2).

NO, SO2, and H2S gases were detected in any of the hospital departments included in the research.CO gas was detected in 11 of all measurements. The median of the CO gas value of the measurements in which CO gas was detected was recorded as 6.00 (4.00-7.00) ppm. All 11 measurements that detected CO gas were conducted at the new campus. Of these, 4 were recorded in social areas, 3 in technical-support units, 2 in outpatient clinics, and 2 in laboratories. Comparison of CO gas levels by hospital units was statistically different (p=0.009). This difference was due to the fact that the CO gas levels measured in the social areas were higher than in the other sections. CO gas measurements in the new hospital campus were statistically significantly higher than the measurements in the old hospital campus (p=0.009). When the CO measurements were examined according to the standards, a CO gas value over 9 ppm was detected in the canteen and the medical device unit in the new campus.

The median of the CO2 gas value in all measurements was 500.00 (300.00-600.00) ppm. Comparison of CO2 gas measurement values according to hospital units was statistically significantly different (p=0.001). The reason for this difference was that the CO2 levels measured in the laboratories were lower than the CO2 levels measured in the outpatient clinic, inpatient clinic and social areas (p value; p=0.005, p=0.005, p=0.030, respectively). A statistically significant difference was found in CO2 gas levels measured in hospital units according to hospital campus (p=0.002, Figure 1C). In 6 of the measurements, the CO2 gas level was determined as 1000 ppm and above, and it was noted that it did not comply with the standards.

There were 442 participants in the study, 292 of whom were hospital staff and 150 patients and their relatives. 53.2% of the participants were women and 66.3% were married. 81.7% of the participants were in the new hospital campus and 18.3% were in the old hospital campus. It was determined that 22.2% of the participants had at least one chronic disease, 23.1% were smokers, and 56.7% have had a respiratory tract infection at least once in the last 1 year.

It was determined that 63.8% of all participants had stress-tension, 45.7% had sleepiness, and 44.8% had headache complaints. 69.8% of those with dysesthesia, 64.6% of those with headache, and 52.8% of those with stress-tension were both in the hospital and outside the hospital. The presence of stress-tension was higher in hospital workers than in patients/patient relatives

Table 1. Evaluation of particulate matter level measurements

	Particulate matter, median (1-3. quartile)
0.3 µm (p/m³)	526.28 (326.41-1208.25)
0.5 µm (p/m³)	139.67 (85.48-300.32)
1.0 µm (p/m³)	27.90 (17.96-48.06)
2.5 µm (p/m³)	6.22 (3.97-9.36)
5.0 µm (p/m³)	1.37 (0.82-2.42)
10.0 µm (p/m³)	0.65 (0.39-1.10)

Table 2. Evaluation of the opinions of hospital staff and patients/ patients' relatives regarding indoor conditions

	Hospital Staff (n=292)	**Patient/Patient relatives (n=150)**
	n (%)	n (%)
Does the atmosphere of the environment bother you when you first enter the hospital?	249 (85,3)	43 (71,3)
Do you go outside to get some air while you work?	292 (100,0)	122 (81,3)
Too little air intake	254 (87,0)	64 (42,2)
Too ventilated	164 (56,2)	30 (20,0)
Too dry	234 (80,1)	44 (29,3)
Too humid	115 (39,4)	7 (4,7)
So hot	226 (77,4)	64 (42,7)
Very cold	209 (71,6)	11 (7,3)
Very bright	192 (66,0)	65 (43,3)
Too dim	1179 (61,3)	20 (13,3)
Dusty	190 (65,1)	21 (14,0)
Airless/closed	235 (80,5)	39 (26,0)
Unpleasant odor is present	232 (79,5)	30 (20,0)
Busy	266 (91,1)	76 (50,7)

(p=0.025). The complaints of dyspnea, headache, stress-tension, itching-burning in the eyes were less common in hospital staff than patients/patient relatives outside the hospital (p=0.001).

The responses of hospital staff and patients/patients' relatives to the statements evaluating the internal environment are summarized in Table 2. 81.3% of the patients/patient relatives included in the research stated that they wanted to open windows in the hospital, and 50.7% stated that the hospital was crowded. Participants working in the old hospital campus stated that they perceived their environment as 'occasional cold' at a lower rate compared to the employees in the new campus (p=0.033). Other

Table 3. Evaluation of the symptoms in the hospital staff and patients/ patients' relatives about the indoor environment conditions

	Hospital Staff (n=292)	**Patient/Patient relatives (n=150)**
	n (%)	n (%)
Sweating	224 (76,7)	71 (47,3)
Chill	205 (70,2)	19 (12,7)
Sleeping state	233 (79,8)	79 (52,7)
İnability to concentrate	227 (77,7)	43 (28,7)
Cough	147 (50,3)	24 (16,0)
Burning, sore throat	169 (57,9)	21 (14,0)
Sneeze	208 (71,2)	26 (17,3)
Dry mouth and nose	215 (73,6)	55 (36,7)
Runny nose	173 (59,2)	17 (11,3)
Nasal congestion	183 (62,7)	28 (18,7)
Shortness of breath	124 (42,5)	22 (14,7)
Headache	227 (77,7)	57 (38,0)
Dizziness, drowsiness	133 (45,5)	29 (19,3)
Burning eyes, itching	160 (54,8)	37 (24,7)
Nausea	126 (43,2)	16 (10,7)
Dry skin itching	170 (58,2)	38 (25,3)
Tiredness	262 (89,7)	87 (58,0)
Overwhelmed by the ambient air	248 (84,9)	77 (51,3)

internal environment perception assessments were similar in hospital staff in both campuses.

The rate of the patient/patient relatives in the old campus perceiving the ambient air uncomfortable, finding the environment too dry, too hot and crowded was higher than the patients/patient relatives in the new campus (p values were respectively; p=0.015, p=0.020, p). =0.032, p=0.018). The frequency of complaints of hospital staff and patients/patients' relatives participating in the research according to their internal environment is presented in Table 3. Statistically significant difference was not found when all internal complaints of the hospital staff were compared according to the old and new campuses of the hospital.

Discussion

According to a research conducted with 360 measurements in 12 different departments of a hospital in Slovenia, the median air temperature was 22.1 °C, the lowest temperature was 19.1 °C, and the highest air temperature was 25.7 °C. It was determined that 55.3% of all measurements were not at the recommended temperature value and the temperature value was statistically different between the sections (17). In this research, the indoor air temperature was found

compatible with the literature. The high temperature measurements in inpatient clinics may be associated with the high circulation of both personnel and patient/patient relatives in inpatient clinics and the infrequent opening of windows. The low temperature values measured in social areas may be associated with the presence of these environments in the hospital entrance and basement floors, and the excessive ventilation of the environment due to the concern of COVID-19 infection transmission.

In a research conducted in 14 geriatric hospitals in Norway, the median indoor relative humidity level was found as 24% (17-26) (18). In this research, the relative humidity level was lower than in other studies. It was determined that humidity measurements made in the operating room and laboratories were lower than in other units. Since laboratories and operating rooms are critical points in the transmission of infectious agents, these areas do not have windows opening to the outside environment or the windows are not opened much and ventilation systems are operated more intensively than other units. It was considered that the absence of natural ventilation may cause the environment to be drier and the humidity measurements to be lower than other units.

In a research conducted in a hospital in Scotland, the average of indoor airflow velocity measurements was 0.056±0.008 m/s, and the airflow was insufficient in all patient rooms (19). In this research, it was determined that the level of airflow velocity measurement complied with the literature. It was considered that the low airflow velocity in all areas where the research was conducted and in the closed areas examined in the literature was caused by the ignoring of the air flow velocity by the indoor users in order to provide thermal comfort.

In a research conducted in different parts of a hospital in Iran, indoor lighting levels were measured at levels ranging from 93 lux to 9946 lux. It has been shown that there is a difference in lighting levels between hospital departments. It was determined that 52.2% of more than 90 measurements were below the standards (20). The illumination level measured in this research was lower in compliance with the standards compared to the literature. The large areas of hospital environments, basements, and the presence of windowless areas can cause daylight not to reach all areas adequately. It was thought that not preferring to turn on the light during daylight might cause the lighting level in hospital interiors to be insufficient.

According to the research conducted in a public hospital with 82 measurements, it was determined that the areas, of which particulate matter level was examined, belong to ISO 7 or ISO 8 class (21). Although all indoor environments in this research were not indoor environments designated as clean rooms, it was determined that the indoor environments in this research belonged to ISO class 5, and they were cleaner than the areas where other studies were carried out. It was considered that the effective and sufficient ventilation systems used in the areas where this research was conducted may have caused the current result.

In a research conducted in a university hospital in Tokyo, the average indoor NO gas level was 34.4±35.0 ppb, and the SO2 gas level was 33.8±2.9 ppb on average, in accordance with the standards (22). In a research conducted by Akova et al. in 3 different hospitals, NO, H2S, SO2 gases were not detected in indoor environments (23). As a result of the measurements in this research, it was determined that there was not NO, H2S and SO2 gas in the indoor environment of the hospital.

In a research examining indoor air quality in 7 different departments of 37 different hospitals in Taiwan, the average CO was found as 2.7±1.2 ppm. In this research, it was determined that CO levels were not different according to hospital units (24). In this research, the places with high CO gas levels was determined were the canteen and medical device unit. Cooking in the canteen, burning an oven, and the lack of central ventilation and outside windows in the medical device unit may have caused this level to be high.

In a research examining the indoor air quality of 17 different polyclinics in Sanlıurfa, the CO2 level of the polyclinics was measured above 1000 ppm in 13 polyclinics and it was found above the standards (25). In this research, it was determined that most of the CO2 gas measurements complied with the standards. It was considered that the good ventilation systems of the hospital where the research was conducted and the low level of air pollution at the location of the hospital caused the low gas measurements.

In a research of 3811 staffs in Finnish hospitals that examined symptoms attributed to indoor air, 25% of participants had nasal irritation, 23% had eye irritation, and 21% had fatigue(26).In a multicenter research conducted with 28,862 participants in office, school and health care settings in Finland, 55.7% of the health professionals, who evaluated the indoor environments they were in, stated that the environment was stuffy and 49.9% found it dry (27).In this research the rates of health complaints related to the indoor environment were different, as in some of the previous studies on indoor air quality. Many factors such as the location of the building, its infrastructure, ventilation, air conditioning, the materials used in its construction, the chemicals and pollutants in it and the number of people affect the indoor air quality and therefore, the complaints of the individuals in the indoor environment. The fact that these research in the literature were carried out in different buildings in different countries can be shown as the reason for this difference.

Conclusion

It was determined that most of the indoor air temperature measurements were in accordance with the standards. It was determined that most of the measured humidity, air flow velocity and lighting levels were not in accordance with the standards. It

was determined that all indoor environments belong to ISO 5 class in clean room classification. After indoor gas measurements (NO, H2S, SO2 gases) were made in the hospital, CO gas was detected in 2 parts of the hospital. It was determined that indoor CO2 level measurements were low and almost all of them were in compliance with the standards. The most common complaints of the hospital staff related to the internal environment of the hospital were determined as fatigue, suffocation from the ambient air, dysesthesia, inability to concentrate, headache, sweating, and dryness in mouth and in nose. The most common complaints related to the indoor environment of the patient/patient relatives were similar to those of the hospital staff; fatigue, dysesthesia, suffocation from ambient air, sweating and headache.

Abbreviations

NO: Nitrogen Oxide

H2S: Hydrogen Sulfide

SO2: Sulfur Dioxide

CO: Carbon Monoxide

CO2: Carbon Dioxide

ISO: International Organization for Standardization

ASHRAE: American Society of Heating, Cooling and Air Conditioning Engineers

PM: Particulate Matter

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Authors' contributions

GE, LSD: conception and design of the study and drafting the article. GE: collection of data and field work. All authors (GE, LSD) participated in the analysis and interpretation of data in addition to writing the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data set produced during the current study is available on reasonable request

Declarations

Ethics approval and consent to participate

Declaration of competing interests

Study principles were approved by Necmettin Erbakan University, Meram Faculty of Medicine Local Ethics Committee (Decision number: 2021/3120), written permission from Meram Medical Faculty Hospital Chief Physician, and informed consent form from the participants were obtained for the study.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Evaluation of Trimethylamine N-Oxide (TMAO) Levels in Blunt Thoracic Trauma: An Experimental Study

Künt Toraks Travmasında Trimetilamin N-Oksit (TMAO) Düzeylerinin Değerlendirilmesi: Deneysel Bir Çalışma

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ABSTRACT

Background/Aim: Thoracic traumas cause life-threatening problems ranging from pulmonary contusion to multi-organ injuries. One of the most common complications of these traumas is acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). It is important to establish a biochemical marker to determine the severity of traumatic injuries and to monitor the inflammatory process. In this study, we aimed to measure the serum concentration of trimethylamine N-oxide (TMAO) and to investigate the diagnostic value of this metabolite in a low (3.31 joules), medium (6.62 joules) and high energy (9.93 joules) model of blunt thoracic trauma in rabbits.
Material and methods: In this study, 27 New Zealand rabbits were divided into four groups: Control, low energy trauma group, medium energy trauma group, and high energy trauma group. Blood samples were collected at 1st , 12th and 24th hours after thoracic trauma.
Results: Statistically significant differences in TMAO levels were found both within and between groups ($p<0.0001$).
Conclusion: TMAO levels increased especially in the first hour following trauma and decreased at 12th and 24th hours compared to the first hour (in moderate and high energy trauma groups). These findings suggest that TMAO levels may be related to the severity and timing of trauma. In ALI resulting from blunt thoracic trauma induced at different energy levels, TMAO levels varied between groups and were associated with the timing and severity of trauma. These findings suggest that TMAO levels may be valuable in evaluating the prognosis of trauma and monitoring the inflammatory process.

Keywords: Acute lung injury; Trimethylamine N-oxide; Biomarker; Trauma

ÖZ

Arka plan/Amaç: Toraks travmaları, akciğer kontüzyonundan çoklu organ yaralanmalarına kadar yaşamı tehdit eden problemlere yol açabilir. Bu travmaların yaygın komplikasyonlarından biri de akut akciğer hasarı (ALI) ve akut solunum sıkıntısı sendromu (ARDS) olarak bilinir. Travmatik yaralanmaların şiddetini belirlemek ve inflamatuar süreci izlemek için biyokimyasal bir belirteç oluşturmak önemlidir. Bu çalışmada, tavşanlarda düşük (3,31 joule), orta (6,62 joule) ve yüksek enerjili (9,93 joule) künt toraks travması modelinde serum Trimetilamin N-oksit (TMAO) düzeylerini ölçmek ve bu metabolitin tanısal değerini araştırmak amaçlanmıştır.
Gereç ve Yöntemler: Bu çalışmada, 27 Yeni Zelanda tavşanı dört gruba ayrıldı: kontrol, düşük enerjili travma grubu, orta enerjili travma grubu ve yüksek enerjili travma grubu. Kan örnekleri toraks travmasından sonraki 1., 12. ve 24. saatlerde alındı.
Bulgular: TMAO düzeyleri açısından hem gruplar içinde hem de gruplar arasında istatistiksel olarak anlamlı farklar bulundu ($p<0.0001$).
Sonuç: TMAO seviyeleri, özellikle travmayı takip eden ilk saatte yükselmekte, 12 ve 24. saatlerde ilk saate kıyasla düşmektedir (orta ve yüksek enerjili travma gruplarında). Bu bulgular, TMAO düzeylerinin travmanın şiddeti ve zamanlamasıyla ilişkili olabileceğini göstermektedir. Farklı enerji seviyelerinde oluşturulan künt toraks travması sonucunda ALI'de, TMAO seviyeleri gruplar arasında değişiklik göstermiş ve travmanın zamanlaması ve şiddetiyle ilişkilendirilmiştir. Bu bulgular, TMAO düzeylerinin travmanın prognozunu değerlendirmekte ve inflamatuar süreci izlemekte değerli olabileceğini düşündürmektedir.

Anahtar Kelimeler: Akut akciğer hasarı, Trimetilamin N-oksit, Biyobelirteç, Travma.

Introduction

Thoracic trauma causes considerable health, social and economic problems and is widespread in society. Severe thoracic trauma accounts for about one third of all trauma patients treated in hospital. These injuries affect an area of the body containing vital organs such as heart and lungs and contribute to 25% of all deaths from traumatic injury (1). Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are conditions of sudden respiratory failure associated with lung fluid accumulation in the lungs due to increased permeability of the membrane between the alveoli and the blood vessels (2). Both ALI and ARDS can occur as a complication of physical injury (3). Trimethylamine N-oxide (TMAO) is a metabolite formed in the human body by the oxidation of trimethylamine by hepatic enzymes (4). TMAO is associated with atherosclerosis and has been the subject of toxicological and clinical interest due to its potential health effects (5, 6). TMAO has been reported to cause atherosclerosis via several mechanisms, including decreased bile acid

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biosynthesis, altered reverse cholesterol transport, foam cell formation, and cholesterol accumulation in macrophages (7). TMAO has also been shown to contribute to heart failure and lead to local and systemic inflammatory reactions (8). In addition, TMAO is associated with the impairment of endothelial nitric oxide (NO) synthase activity, which promotes oxidative stress and inflammation (9). TMAO is associated with triggering chronic inflammatory responses that lead to cerebrovascular disease (10).

In summary, TMAO plays an important role in modulating inflammatory responses, particularly in the context of cardiovascular health, atherosclerosis and other health conditions. Considering that bilateral blunt thoracic trauma is also an inflammatory process, it is likely to be associated with TMAO levels. Nevertheless, there is a lack of research investigating this relationship. It is important to investigate whether TMAO can serve as a biomarker to predict which ALI patients might progress to severe ARDS requiring prolonged ventilator support, and which might develop pulmonary fibrosis and ultimately face death. However, current studies are insufficient for the routine use of biomarkers that indicate the severity of injury thoracic trauma.

The aim of our study was to measure serum TMAO levels and investigate the diagnostic value of TMAO in an experimental model of low, medium, and high energy blunt thoracic trauma in rabbits.

Material And Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of ***, Experimental Medicine Research and Application Center (protocol code 2022-39 and date of approval 30/09/2022) for studies.

Experimental Model

The study was conducted on 27 New Zealand rabbits aged 1 to 2 years, bred at the Experimental Animal Research Center of *** University.

Control group (n=6): No trauma was administered to this group during the experiment. Blood samples were taken after 1st, 12th and 24th hours. As the venous vascular system was not anatomically suitable for blood sampling due to the administration of fluid and medication via the venous route, both the arterial and venous routes were used. After 24 hours, the subjects were sacrificed.

Low energy trauma group (n=7): Low energy trauma (3.31 joules) was inflicted on the rabbits in this group without blood sampling. After the trauma, blood samples were taken after 3 hours as in the control group and the subjects were then sacrificed.

Medium energy trauma group (n=7): Medium energy trauma (6.62 joules) was administered prior to blood collection, and samples were collected at three different time points post-trauma during the experiment. After 24 hours, the subjects were sacrificed.

High energy trauma group (n=7): Blood samples were collected after the application of trauma (9.93 joules). After 24 hours, the subjects were sacrificed.

Anesthesia and Trauma Model

All traumatized subjects were anesthetized with 40 mg/kg ketamine HCl (Ketalar) and 10 mg/kg xylazine HCl (Rompun) administered intramuscularly into the hind leg of the rabbit. The bilateral blunt thoracic trauma model previously used in other studies was modified. The low, medium and high energy trauma groups were subjected to the same model with the addition of a variable weight. Using the bilateral blunt thoracic trauma model, weights of 250 g, 500 g and 750 g were dropped from a height of 0.62 meters onto the lateral wall of the thorax for the low, medium and high energy trauma groups. The resulting energy was calculated using the formula E= mgh (where E is energy, g is gravity at 10 m/s², h is height at 62 cm, and m is the weight dropped at 0.25 kg, 0.50 kg, and 0.75 kg). Accordingly, the energy transferred to the chest wall was determined as 3.31 joules (low energy), 6.62 joules (medium energy), and 9.93 joules (high energy), assuming a frictionless scenario. After 24 hours, the surviving subjects were sacrificed with a sedation dose that was twice that of the original anesthesia (11).

Biochemical analysis

Blood samples taken after at 1st, 12th and 24th hours were stored at -80°C until analysis. To determine the TMAO content, the previously prepared serum samples were thawed at room temperature and analyzed using an LC-MS/MS instrument (ABSciex API 3200 tandem mass spectrometer) in the biochemistry laboratory of the *** University Faculty of Medicine. In brief, each tube received the TMAO isotope, followed by the addition of 100% methylene hydroxide as a precipitant. After all tubes were gently shaken for 30 seconds, they were centrifuged at 14,000 rpm for 10 minutes. The supernatant of the samples was then transferred to clean tubes. The tubes were evaporated under nitrogen gas at 28°C. The samples were reconstituted with 100% water. After centrifugation at 4,500 rpm for 10 minutes, the supernatant was collected and transferred to vials compatible with the LC-MS/MS instrument. The TMAO concentrations in the samples were determined against the TMAO standard in the LC-MS/MS instrument using two mobile phases. The results obtained were statistically analyzed.

Statistical analysis

All statistical analyses were performed with the software R version 3.6.0. The normality of the data was checked using the Shapiro-Wilk normality test. The variables were expressed as mean ± standard deviation. One-way analysis of variance or the Kruskal-Wallis test was used to compare the measured parameters between the groups. The Tukey HSD test or the DSCF post hoc test with Bonferroni correction was used for the pairwise comparison of the parameters. In addition, repeated measures analysis of variance or Friedman test was used for comparison of parameters

between measurement time points in each group and pairwise comparisons were performed using Bonferroni confidence intervals or Durbin-Conover post hoc tests. The statistical significance level was set at p<0.05.

Results

The study included 27 rabbits divided into four groups: a control group (n=6), a low energy trauma group (n=7), a medium energy trauma group (n=7), and a high energy trauma group (n=7).

In terms of temporal comparison within groups, serum TMAO levels decreased significantly at 12th hour (107.47 ± 14.00) and at 24th hour (89.97 ± 2.34) in the medium energy trauma group compared to levels at 1st hour (176.29 ± 7.13) (p<0.0001). Similarly, TMAO levels decreased significantly in the high energy trauma group at 24th hour (172.86 ± 20.09) compared to 1st hour (310.29 ± 50.23) and 12th hour (241.00 ± 26.64) after trauma (p=0.028) (Table 1).

Comparison between the groups: At the 1st hour, TMAO levels were lower in the low energy trauma group than in the control group, the medium energy trauma group, and the high energy trauma group (p<0.0001). At 12th and 24th hours, TMAO levels were significantly lower in the low and medium energy trauma groups than in the control group (p<0.0001). In addition, TMAO levels were higher in the high energy trauma group than in the medium energy trauma group (p<0.0001) (Table 1). Figure 1 also summarizes the change in TMAO levels within the groups as a function of time.

Table 1. Laboratory values of the experimental groups depending on time and trauma level.

Biomarker	Groups	Time			p-value (Within groups)
		1st hour	12th hour	24th hour	
TMAO (ng/ml)	Control group	201.33 ± 10.99^{a}	162.00 ± 5.81^{a}	211.67 ± 19.28^{a}	0.070
	Low energy trauma group	126.11 ± 10.63^{b}	105.34 ± 9.13^{b}	115.66 ± 13.63^{b}	0.410
	Medium energy trauma group	176.29 ± 7.13^{a}	107.47 ± 14.00^{Ab}	89.97 ± 2.34^{Bb}	<0.001
	High energy trauma group	310.29 ± 50.23^{a}	241.00 ± 26.64^{a}	172.86 ± 20.09^{BCa}	0.028
	p-value (Between groups)	<0.001	<0.001	<0.001	

Data were expressed as mean ± standard error of the mean.

A shows comparison 1st vs. 12th hour.; B shows comparison 1st vs. 24th hour.; C shows comparison 12th vs. 24th hour.

Different small superscripts letters in each column indicate that statistically significant difference between two groups after pairwise comparisons.

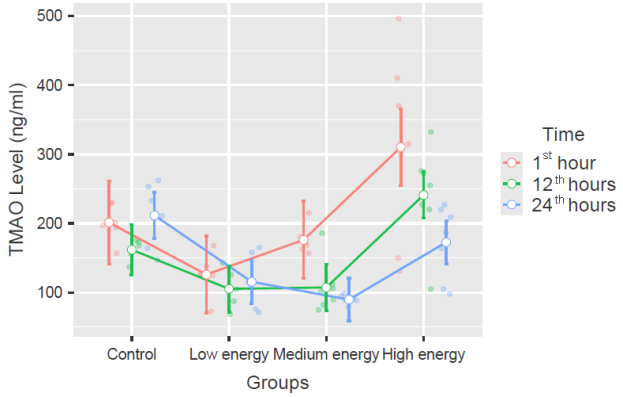

Figure 1. The graph shows the changes in the TMAO (ng/ml) for four different groups (control, low energy trauma group, medium energy trauma group, and high energy trauma group) according to three different times (1st , 12th , and 24th hours)

Discussion

This study is the first to evaluate the relationship between trauma severity, timing of trauma, and TMAO. The results support the hypothesis that TMAO levels may be useful in assessing the prognosis of trauma and monitoring the inflammatory process.

Thoracic trauma causes life-threatening problems ranging from pulmonary contusion to multi-organ injury, while ALI and ARDS are common complications of traumatic injury (12). The aim of our study was to measure TMAO levels to determine the lung damage caused by low, medium, and high blunt thoracic trauma in rabbits and to investigate the diagnostic and prognostic value of TMAO. A recently developed trauma model was used to investigate the degree of lung injury and the natural pulmonary inflammatory response in rabbits (11). This model is clinically similar to lung injury after blunt thoracic trauma.

Pulmonary contusion, a common consequence of blunt trauma to the chest, is characterized by localized pulmonary injury and inflammation. The mechanical forces applied during trauma trigger oxidative stress, the formation of reactive oxygen species, leukocyte infiltration and the release of inflammatory cytokines. This cascade of events can induce a systemic inflammatory response and impair endothelial function while contributing to the initiation and potentiation of the inflammatory process (13, 14). Tissue damage and inflammation caused by trauma can affect the gut microbiota and increase TMAO production (15). TMAO is a biologically active molecule that plays a role in the development of diseases such as thrombosis, stroke, heart disease, type 2 diabetes, obesity, especially atherosclerosis (5, 16). In the context of vascular health, TMAO has been associated with the exacerbation of vascular inflammation and oxidative stress, leading to endothelial dysfunction and atherosclerosis (4). In the study by Brunt et al., TMAO was shown to cause age-related endothelial dysfunction through oxidative stress (17). Sun et al. have shown that TMAO significantly triggers oxidative stress, dose- and time-dependent release of inflammatory cytokines, and inhibition of endothelial NO synthase and NO production. Therefore, increased TMAO levels are associated with decreased NO bioavailability as an inhibitor of NO

synthase and thus disease severity (18). According to the data, TMAO levels were elevated in the first hour after trauma and in the medium and high energy trauma groups. No significant difference was found in the low energy trauma group. The lack of a significant difference can be attributed to the low intensity of the trauma applied, which resulted in the absence of the expected effect in the animals. Considering the studies, since endothelial dysfunction caused by NO depletion and the concomitant inflammatory process may lead to the release of inflammatory markers in the body, an increase in TMAO was observed in relation to the severity and timing of the trauma. Administration of low dose NO attenuated oxidative stress and inflammatory lung injury in the ALI rabbit model (19).

In trauma research, there is a growing interest in understanding the molecular and metabolic changes that occur after traumatic events. Metabolic profiling has revealed changes in urinary TMAO concentrations following surgical trauma, indicating its potential as a biomarker of surgical stress and trauma (20). Ina addition, the inflammatory response following severe traumatic brain injury has been shown to modulate the kinetic profile of inflammatory markers, highlighting the complex interplay between trauma and the immune system (21). TMAO, a microbial metabolite from the gut, is known to play an important role in immune responses, inflammatory processes and various diseases (22, 23).

TMAO has been associated with the promotion of vascular inflammation and endothelial dysfunction, which are critical components of the pathophysiologic response to ALI (24). In addition, TMAO has been associated with cardiovascular risk and unfavorable outcomes in patients with acute myocardial infarction and stroke, indicating its potential influence on systemic inflammatory responses and tissue damage (25).

The effects of TMAO on inflammation extend to various aspects of vascular health, gut microbiota, and regulation of inflammatory mediators, highlighting its potential as a key factor in the pathogenesis of inflammation-related diseases (26). Although there are no studies investigating this relationship, it is hypothesized that there is an association between TMAO levels and bilateral blunt chest trauma, as it is an inflammatory process. And the results showed significant differences in TMAO levels between different energy levels and time points, suggesting a possible relationship with the severity and progression of the trauma. In particular, in the medium and high energy level groups, the elevated TMAO levels in the first hour after trauma possibly indicate an acute phase response and the severity of the injury. The subsequent decrease after 12th and 24th hours can indicate the subsiding of the acute response. TMAO has the potential to serve as a biomarker for predicting various outcomes in patients with ALI, such as the development of severe ARDS, the need for prolonged ventilatory support, the occurrence of pulmonary fibrosis and ultimately mortality. However, the study evidence is not yet sufficient for the routine use of the TMAO biomarker to indicate the severity of injury following chest trauma. Future studies focusing on the interaction between TMAO and blunt chest trauma are needed to improve our understanding of potential biomarkers associated with this type of trauma.

Limitations of the study: TMAO may be associated with the severity of trauma and the patient's prognosis in the early phase of trauma. While it is hypothesized that it can be used as a biomarker, the fact that we do not have enough information on the prognosis of the animals included in the study, as the study was terminated early (24 hours after trauma), is considered an important limitation. Further studies on this topic are needed.

Conclusion

TMAO has been associated with numerous pathophysiologic conditions, most notably atherosclerosis, and it is likely that it is also associated with trauma. Blunt thoracic trauma is an important cause of injury and death, often leading to various thoracic complications and concomitant injuries. Therefore, biomarkers such as TMAO are valuable tools for understanding the physiological and psychological effects of trauma. We believe that the determination of TMAO levels in our study can help to evaluate the prognosis of trauma and monitor the inflammatory process. We believe that further studies should be conducted to substantiate these ideas. To our current knowledge, this is the first study in this field.

Declarations

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Declaration of Competing Interest

The authors declare that they have no conflict of interest..

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None.

Data Availability

The data sets generated during or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Selçuk, Experimental Medicine Applications and Research Centre (protocol code 2022-39 and date of approval 30/09/2022) for studies.

Author Contributions

Conception: B.O., A.B., H.K., F.A., H.V., Data Collection and Processing: B.O., A.B., H.K., Design: : F.S., F.A., B.O., H.V., Supervision: B.O., Analysis and Interpretation: F.S., F.A., M.K.K., Literature Review: F.S., F.A., H.V., Writer:

F.S., M.K.K., Critical Review: F.S., F.A., B.O., H.V., A.B., H.K., M.K.K.

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ORIGINAL ARTICLE

Investigation of Insulin-Like Growth Factor 2 mRNA Binding Protein 2 Gene Polymorphisms in Type 2 Diabetes Patients

Tip 2 Diyabet Hastalarında İnsülin Benzeri Büyüme Faktörü 2 mRNA Bağlayıcı Protein 2 Gen Polimorfizmlerinin Araştırılması

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ABSTRACT

Background/Aim: Genome-Wide Association Studies (GWAS) have reported that polymorphisms (rs1470579 and rsS4402960) in Insulin Like Growth Factor 2 mRNA Binding Protein 2 (IGF2BP2) gene partially increase the risk of Type 2 Diabetes (T2D). The aim of this study was to investigate the association of IGF2BP2 variants rs4402960 and rs1470579 with T2D in Turkish population.
Material and Methods: For IGF2BP2 rs1470579 and rs4402960 SNPs (Single Nucleotide Polymorhism), genotyping of 200 individuals (100 healthy individuals and 100 T2D patients) was performed by RT-PCR method (Applied Biosystems). Relationships of genotypes and alleles frequency of IGF2BP2 polymorphisms and T2D were examined by "Chi-square" or "Likelihood ratio" tests.
Results: When evaluated in terms of genotype and allele distributions; for IGF2BP2 rs1470579 (A/C), an association was found between T2D patients and healthy individuals (p= 0.0123) and individuals with AC genotype in the patient group were more than healthy individuals. For IGF2BP2 rs4402960 (G/T), there was no difference in genotype distribution between T2D patients and control group (p= 0.8205).
Conclusion: Our study showed that IGF2BP2 gene rs1470579 polymorphism was associated with T2D in the Turkish population (p<0.05). Furthermore, this is the first study to analyze the relation between IGF2BP2 gene polymorphisms and T2D in the Turkish population.

Keywords: IGF2BP2, T2D, Polymorphism

ÖZ

Amaç: Genom çapında ilişkilendirme çalışmaları (GWAS) İnsülin Benzeri Büyüme Faktörü 2 mRNA Bağlayıcı Protein 2 (IGF2BP2) genindeki rs1470579 ve rs4402960 polimorfizmlerinin Tip 2 diyabet (T2D) riskini kısmen arttırdığını bildirmiştir. Bu çalışmanın amacı, Türk toplumunda rs4402960 ve rs1470579 IGF2BP2 varyantlarının T2D ile olan ilişkilerini araştırmaktır.
Gereç ve Yöntem: IGF2BP2 rs1470579 ve rs4402960 SNP'leri (Single Nucleotide Polymorhism) için 100 sağlıklı birey 100 T2D hastası olmak üzere 200 bireyin genotipleme çalışması RT-PCR yöntemiyle gerçekleştirildi (Applied Biosystems). IGF2BP2 polimorfizmlerinin genotip ve allel sıklığı ile T2D arasındaki ilişkiler "Ki-kare" veya "Olabilirlik oranı" testleri ile incelenmiştir.
Bulgular: Genotip ve allel dağılımları açısından değerlendirildiğinde; IGF2BP2 rs1470579 (A/C) için T2D hasta ile sağlıklı bireyler arasında ilişki bulunmuş olup (p= 0.0123) hasta grubunda AC genotipine sahip olan bireyler sağlıklı bireylerden daha fazladır. IGF2BP2 rs4402960 (G/T) için ise, T2D hastaları ve kontrol grubu arasında genotip dağılımı açısından bir fark yoktur (p= 0.8205).
Sonuçlar: Çalışmamız, IGF2BP2 geni rs1470579 polimorfizminin Türk toplumunda T2D ile ilişkili olduğunu göstermiştir (p< 0.05). Ayrıca bu çalışma, Türk toplumunda IGF2BP2 gen polimorfizmleri ile T2D arasında yapılan ilk çalışmadır.

Anahtar Kelimeler: IGF2BP2, T2D, Polimorfizm

Introduction

Type 2 Diabetes accounts for about 95% of the diabetic population, although prevalence varies in different populations (1). Today, T2D, a chronic metabolic disorder with increasing cardiovascular morbidity and mortality, is recognized as one of the growing epidemics worldwide (2). Also, the addition of environmental factors and genetic components has led to an increase in the prevalence of the disease (3). Many factors such as high plasma glucose levels resulting from the combination of insulin resistance and deficiency, the course of blood sugar level, changes in lipid metabolism and platelet dysfunction lead to complications in T2D (4,5).

Genome-wide association and linkage-based studies have defined a large number of SNPs associated with T2D (6). The genes involved in glucose transport, blood glucose homeostasis, beta cell function, insulin secretion, and pancreatic developmental pathways are considered to be excellent candidates in T2D ethology (7-10). The IGF2BP2 gene has been implicated in pancreatic β-cell dysfunction, decreased insulin secretion and activation leading to the development of T2D (10-13).

The IGF2BP2 gene modulates the translation of IGF2 by binding to the 5'-untranslated region of IGF2 mRNA (11-13). The IGF2BP2 gene is located in the q27.2 region of chromosome 3 and has important functions in RNA trafficking, stability and translation (13,14). IGF2BP2 plays a role in pancreatic development and stimulation of insulin secretion by binding to IGF-2, an important growth

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and insulin signalling molecule (12,13). Also, other polymorphisms found in the promoter regions of the IGF2BP2 gene have been associated with adipocyte and insulin resistance. Thus, it has been stated that this gene can change the functions of pancreatic and adipose tissues by affecting the expression of IGF2 and other proteins (13).

Studies have shown that IGF2BP2 variants are associated with impaired beta cell function rather than fasting blood glucose level or decreased insulin sensitivity. One of these, IGF2BP2 gene rs1470579 and rs4402960 SNPs have been found to be associated with the development of T2D in many populations (7-10). Therefore, the aim of our study was to investigate the association of IGF2BP2 variants with T2D in the Turkish population.

Material and Methods

Subjects

The study included 100 patients diagnosed with T2D and 100 healthy controls at Mersin University, Faculty of Medicine, Department of Endocrinology and Metabolic Diseases. The individuals participating in the study were included in the study by approving the informed consent form. Our study was approved and accepted by the Local Ethics Committee of Mersin University Faculty of Medicine (Ethics approval no.: 2012/370).

Genotyping of Polymorphisms in IGF2BP2: DNA Isolation and Analysis

DNA isolation from peripheral blood was performed by kit method. Genomic DNA was isolated from leukocytes using a high purity template preparation kit (Roche, Switzerland) following the manufacturer's protocol. Genotype analysis of IGF2BP2 gene polymorphisms was performed by RT-PCR using the Light Cycler DNA Master Hybridization probes kit. Primer and probe sequences are given in Table 2.

The Assays on Demand SNP genotyping kit was used for RT-PCR (Applied Biosystems, USA). SNP amplification experiments were performed according to the protocol. In brief, 50 µl of reaction solution containing 43 µl PCR grade water, 1 µl (10 pmol/ µl), of each PCR primers,1 µl qPCR pre mix (Taq DNA polimeraz, 10X reaction buffer, dye (xylene cyanole), stabilizer (sorbitol), tween 20, dNTP) and 5 µl of DNA.

Statistical Analysis

Relationships of genotypes and alleles frequency of IGF2BP2 polymorphisms and T2D were examined by "Chi-square" or "Likelihood ratio" tests. "Hardy-Weinberg" balances of the patient and healthy groups were checked in terms of genotypes. Descriptive statistics are presented as frequency and percentage for categorical variables while continuous variables are presented as mean ± standard deviation.

According to the results of our study, odds ratios (OR) and 95% confidence intervals (CI) were calculated to express the risk of T2D in terms of genotype distributions. Variables were considered significant when p-values were less than 0.05, and statistical analysis was performed using SPSS version 11.5 software.

Results

In this study, 100 patients (male= 59, female= 41, mean age: 54.24 ± 16.52) and 100 controls (male= 56, female= 44, mean age: 51.32 ± 14.82) were studied (Table 1). The polymorphisms of the IGF2BP2 gene (rs1470579 and rs4402960) were determined by the RT-PCR according to the Q-PCR Premix system produced by Bioneer.

When the results were analyzed as percentages in terms of allele frequency, the genotype frequencies of AA, AC and CC genotypes for the rs1470579 SNP in T2D patients and healthy groups were found as 73%, 19% and 8% in controls and 54%, 33% and 13% in T2D patient groups. There was a significant difference in the genotype frequency of IGF2BP2 rs1470579 (A/C) polymorphism between the control group and T2D patients (p= 0.0123; OR; 2.348 (1.21-4.57)) (Table 3). Individuals with AC genotype in the T2D patient group were higher than those with AC genotype in the healthy control group.

When we analyzed the genotype frequencies of T2D patients and control group individuals for rs4402960 polymorphism, the percentages of GG, GT and TT genotypes were 48%, 13% and 39% respectively in controls, while they were 51%, 10% and 39% in T2D patient groups. On the other hand, no difference was found between T2D and control groups in terms of genotype distribution for IGF2BP2 rs4402960 (G /T) gene polymorphisms (p= 0.8205). For TT and GG+GT genotype distribution, no relation was found between T2D patients and control group (p= 0.8847) (Table 4).

Table 1: The number of T2D patient and control groups according to mean age and gender

	Patients	Controls	P value
Number	100	100	
Age(years)	54, 24 ± 16, 52	51,32 ± 14,82	0.189
Female (%)	41	44	0.775
Male (%)	59	56	

Table 2: The sequence of Primers for *IGF2BP2* gene (rs1470579 and rs4402960)

Gene/SNP	Sequences	
IGF2BP2 rs1470579 (A/C)	F	5'- TCCAAACAGCTATCATCATT -3'
	R	5'- ATGAGTGAGAGGGAAAAGTC-3'
IGF2BP2 rs4402960 (G/T)	F	5'- CTGGGGAGCAGTAA -3'
	R	5'- TTGACCATTCCTTATCT -3'

Table 3: Analysis of *IGF2BP2* rs1470579 SNP genotype and allele frequency in control and T2D patients

GENOTYPE IGF2BP2 (rs1470579)	CONTROL N (%)	T2D PATIENTS N (%)	P value	OR (95%CI)
AA	73 (73%)	54 (54%)		Reference range
AC	19 (19%)	33 (33%)	0,0123	2.348 (1.21-4.57)
CC	8 (8%)	13 (13%)		1.196 (0.85-5.67)
ALLELE				
A	165(82.5%)	141(70.5%)	**0.0651**	0.718 (0.68-4.35)
C	35(17.5%)	59 (29.5%)		

Table 4: Analysis of *IGF2BP2* rs4402960 SNP genotype and allele frequency in control and T2D patients

GENOTYPE IGF2BP2 (rs4402960)	CONTROL N (%)	T2D PATIENTS N (%)	P value	OR (95%CI)
GG	48 (48%)	51 (51%)		Referans
GT	13 (13%)	10 (10%)	0.8205	0.724 (0.29-1.80)
TT	39 (39%)	39 (39%)		0.941 (0.52-1.70)
ALLELE				
G	109 (54.5%)	112 (56%)	**0.8847**	1.000 (0.56-1.76)
T	91(45.5%)	88 (44%)		

Discussion

Type 2 diabetes is a metabolic disease manifested by impaired insulin secretion and insulin resistance, in which environmental and genetic factors play a combined role in the development of the disease (14-15).

IGF2BP2 is involved in many biological processes by interacting with miRNAs, mRNAs and long non-coding RNAs to regulate various signalling pathways (16-17). IGF2BP2 gene has been recognized to be linked with reduced secretion of insulin and B cell function (18). Genome-Wide Association Studies (GWAS) have shown that IGF2BP2 gene polymorphisms are also associated with pancreatic β-cell function and hyperglycaemia, and SNPs in the second intron of this gene are critical in the occurrence of T2D (13).

The rs1470579 and rs4402960 in this study are located in intron 2 region of IGF2BP2. SNPs in this intron are thought to affect gene function through possible mechanisms by alternative splicing, protein interaction of IGF2BP2, miRNAs or antisense mRNA transcription, regulation of large noncoding transcription factors. Many genes located near IGF2BP2 are metabolic regulators involved in insulin metabolism (11-14). SNPs may also be directly associated with miRNAs, non-coding transcripts and close variants affecting antisense mRNAs transcribed in intron 2 (11).

IGF2BP2 is widely expressed during the perinatal period and in many adult tissues such as intestine, bone marrow muscle, kidney, lung and brain. In these organs, differences in IGF2BP2 expression may affect feeding behaviour and glucose metabolism, which may influence physical activity or obesity risk and thus the lifetime occurrence of T2D (13). These two polymorphisms (rs4402960 and rs1470579), which are associated with obesity, have also been reported to be involved in low fasting insulin levels and impaired β-cell function (16).

In our study, T2D was significantly related with rs1470579 (A/C) polymorphism between patient and healthy groups (p = 0.0123; OR; 2.348 (1.21-4.57)). Individuals with AC genotype were 2,348 times more likely to be ill than the control group. According to this result, it was determined that having AC genotype increases the risk of T2D in the Turkish population. However, it is not significantly associated with the rs4402960 (G/T) polymorphism (p= 0,8205). When evaluated in terms of TT and GG+GT genotype distribution, no relation was found between T2D patients and healthy individuals (p= 0.8847).

Our results showed the frequency of different genotypes of SNPs in different populations. These polymorphisms have been shown to be associated with T2D in some populations such as Chinese Han Japanese, Moroccan Czech Greek-Cypriot German Icelandic Asian Israeli, Lebanese and Indian Tunisian Arabs (16). In addition, the wild C allele has been reported to be the protective allele against T2D for IGF2BP2 rs4402960 polymorphism in the Chinese Han population (19). A meta-analysis of nearly 176,000 people investigating the association between the IGF2BP2 gene (rs4402960, rs1470579) and T2D found that these SNPs increased the risk of T2D, but that this increase differed between ethnic populations (20).

In our results, we found that the genotype frequencies of rs4402960 polymorphism did not differ between T2D patients and healthy individuals. Grarup et al. (21) conducted a similar study in the Danish population and found no association between IGF2BP2 gene polymorphism and T2D. In this sense, it overlaps with our study. Groenewoud et al. (7) investigated the expression of IGF2BP2 gene SNPs in Dutch and German populations and reported that these SNPs negatively affect insulin secretion in the early stages of diabetes. Moreover, it has been reported that IGF2BP2 polymorphisms may differ in metabolic diseases even in the same ethnic groups. For example, Zhang et al. (22) examined IGF2BP2 gene polymorphisms in 4531 T2D cases and 3807 controls in a large-scale case-control study. They found that IGF2BP2 SNPs had strong relation with T2D in the Chinese Han population (rs1470579 p= 1.80×10 (-7), OR= 1.22, rs4402960 p= 7.46×10 (-9), OR = 1.26). However, this association has not been detected in many GWAS studies in the Chinese Han population (Li et al reported p= 6.5×10−2 for rs4402960, Tsai et al reported p= 0.22, Cui et al reported p= 0.31, Shu et al reported p= 2.4×10−3) (23-26).

Rao et al. (27) found significant correlation between T2D and IGF2BP2 polymorphisms in Asian populations. They conducted a study with 461 T2D patients and 434 healthy individuals on Asians. They found that individuals with the TT genotype at rs4402960 had a higher risk of T2D than carriers of the G allele (TG + GG) (AOR) = 1.962, p = 0.031), and individuals with the CC genotype at rs1470579 were reported to have a higher risk of developing T2D than individuals with the A allele (CA + AA) (AOR = 2.014, p = 0.021).

The IGF2BP2 protein is involved in the metabolic processes of IGF2 and disturbances in these processes can lead to the development of metabolic diseases such as obesity and T2D (14). Considering the results of our study, we found that rs1470579 IGF2BP2 gene polymorphism may be a risk for susceptibility to T2D. This suggests a strong role for IGF2BP2 in susceptibility to T2D. In addition, recent studies have reported that IGF2BP2 dysfunction is implicated in the development and progression of multiple metabolic diseases and cancers, which differ between ethnic populations.

Conclusion

This study was conducted to investigate the association of IGF2BP2 rs4402960 and rs1470579 SNPs with T2D and to determine the genetic predisposition in Turkish population. We showed that IGF2BP2 rs1470579 polymorphism is associated with T2D. This result suggests that people with this heterozygous mutant allele (AC) are at higher risk of developing T2D. Considering that environmental/lifestyle changes may change the risk of T2D, to include these possible factors in the study and to increase the sample size will contribute to further studies.

Information obtained as a result of the study

• We determined the genetic susceptibility of IGF2BP2 on T2D under different genetic variants of IGF2BP2 gene rs4402960 and rs1470579 and investigated the association with T2D in Turkish population.

• We have shown that this IGF2BP2 rs1470579 polymorphism is associated with T2D in the Turkish population. This result suggests that individuals carrying this heterozygous mutant allele (AC) are at greater risk of developing T2D.

• Our study was not adjusted for any covariates such as gender, smoking, alcohol intake. A more comprehensive analysis should be performed by increasing the sample size, replicating this study in different ethnicities and considering interactions between risk factors.

• Clarification of the pathogenesis of T2D is necessary to identify individuals at risk of the disease and to effectively treat patients by elucidating genome-drug interactions.

• Recent meta-analyses and SNP studies will provide an understanding of the genetic factors that play an active role in the development and progression of multifactorial diseases.

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Conflict of Interest

No conflicts of interests were disclosed by the authors.

Abbreviations

T2D: Type 2 diabetes

IGF2BP2: Insulin-like Growth Factor 2 mRNA Binding Protein 2 Gene

SNP: Single Nucleotid Polymorphism

PCR: Polymerase Chain Reaction

GWAS: Genome-Wide Association Studies

BMI: Body Mass Index

OR: Odds ratio

AOR: Adjusted Odd Ratio

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ORIGINAL ARTICLE

Evaluation of Quality of Life and Health Literacy in Women Receiving Infertility Treatment

İnfertilite Tedavisi Gören Kadınlarda Yaşam Kalitesi ve Sağlık Okuryazarlığının Değerlendirilmesi

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ABSTRACT

Background: Infertility and its treatment can be complex, difficult, and uncomfortable, especially for women. Therefore, it is important to evaluate the quality of life and health literacy of women. This study was conducted to evaluate the quality of life and health literacy in women receiving infertility treatment and to determine the relationship between them.
Methods: The study, in which a descriptive design was used, was carried out with 186 women who received infertility treatment. Data were collected by a descriptive information form, the Fertility Quality of Life Questionnaire (FertiQoL), and the Turkiye Health Literacy Scale-32 (THLS-32).
Results: The mean scores of participants were 61.73±16.71 on the total FertiQoL and 36.46±8.45 on the total THLS-32. The level of health literacy was inadequate in 7.5% of women, problematic/limited in 28.5%, adequate in 31.7%, and excellent in 32.3%. There was no significant correlation between FertiQoL and THLS-32 scores (p>.05).
Conclusion: In this study, it was determined that the quality of life and health literacy of women who received infertility treatment were not at the desired level. The study found no relationship between women's quality of life and health literacy.

Keywords: infertility, quality of life, health literacy, women

ÖZ

Giriş: İnfertilite ve tedavisi özellikle kadınlar için karmaşık, zor ve rahatsız edici olabilir. Bu nedenle kadınların yaşam kalitesinin ve sağlık okuryazarlığının değerlendirilmesi önemlidir. Bu çalışma infertilite tedavisi gören kadınlarda yaşam kalitesi ve sağlık okuryazarlığının değerlendirilmesi ve aralarındaki ilişkinin belirlenmesi amacıyla yürütülmüştür.
Yöntemler: Tanımlayıcı desenin kullanıldığı çalışma, infertilite tedavisi gören 186 kadın ile gerçekleştirildi. Veriler; Tanımlayıcı Bilgi Formu, Doğurganlık Sorunu Yaşayan Kişiler İçin Hayat Kalitesi Ölçeği (FertiQoL) ve Türkiye Sağlık Okuryazarlığı Ölçeği-32 (TSOY-32) ile toplanmıştır.
Bulgular: Katılımcıların toplam FertiQoL puan ortalaması 61.73±16.71, TSOY-32 puan ortalaması ise 36.46±8.45 idi. Kadınların sağlık okuryazarlığı düzeyi %7.5'inde yetersiz, %28.5'inde sorunlu/sınırlı, %31.7'sinde yeterli ve %32.3'ünde mükemmel olduğu belirlendi. FertiQoL ile TSOY-32 puanları arasında anlamlı bir korelasyon yoktu (p>.05).
Sonuç: Bu çalışmada infertilite tedavisi gören kadınların yaşam kalitesinin ve sağlık okuryazarlığının istenilen düzeyde olmadığı belirlendi. Kadınların yaşam kalitesi ile sağlık okuryazarlığı arasında ilişki olmadığı saptandı.

Anahtar Kelimeler: infertilite, yaşam kalitesi, sağlık okuryazarlığı, kadın

Introduction

Infertility, which affects 17.5% of the adult population worldwide (1), is a condition that can cause emotional, psychological, and social problems (2). The quality of life of individuals is negatively affected by the diagnosis of infertility in addition to the difficulties experienced during the diagnosis and treatment. The quality of life is lower in infertile individuals than in fertile individuals and women than in men among infertile couples (3). Factors affecting the quality of life of infertile individuals include education level, culture, age, duration of marriage, and menstrual factors of women (3). A systematic review indicated that health literacy was moderately correlated with quality of life (4). However, no study examining the relationship between health literacy and quality of life in infertile women has been found in the literature. Infertile women obtained information from different sources and majority of them (87%) wanted to get more information (5). In a study on the knowledge and resources of female patients attending the infertility outpatient clinic, it was found that 42.5% of participants did not have knowledge about IUI and 70.8% of them did not know about IVF (6). Based on these results, it is thought that it is important to investigate health literacy in women who present to infertility clinics. "Health literacy (HL) represents the personal knowledge and competencies that accumulate through daily activities, social interactions and across generations." (7). HL is associated with access to health information and health behavior (7). In addition, it plays an important role in reproductive information and may affect reproductive behaviors and outcomes (8).

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Some studies in the literature have shown that HL is associated with quality of life in different sample groups (4, 9, 10). However, this study is the first to evaluate the relationship between health literacy and quality of life in infertile women. This study was conducted to evaluate the quality of life and HL in women receiving infertility treatment and determine the relationship between them.

Methods

A descriptive design was used. The population of the research consisted of women receiving treatment in a fertility center. The sample consisted of volunteers who were on treatment between April and June, 2022 in the fertility center and they were literate. Women with a history of chronic and psychiatric diseases, as well as those who were health professionals, were excluded from the study.

G*Power 3.1.9 software was used to determine the sample size. Following a power analysis based on a systematic review that examined the impact of HL on quality of life (4), for a statistical power of 95% and a margin of error of 0.03, the minimum sample size required for inclusion in the study was calculated as 184. However, the target sample consisted of 200 women to prevent data loss and increase validity. Out of these, 11 did not meet the inclusion criteria, and 3 declined to participate. Consequently, our final sample consisted of 186 women.

Data Collection

The data were collected face-to-face at the center where the study was conducted. Data collection forms were provided to the participants, and it was made easier for them to fill out the forms in a room at the center, ensuring their privacy. Study data were collected using a descriptive information form, the Turkiye Health Literacy Scale-32, and the Fertility Quality of Life Questionnaire.

Descriptive Information Form

The form included demographic (age, education, employment status, income status, and duration of marriage) and infertility characteristics (type of infertility, cause of infertility, duration of infertility, and number of treatments).

The Turkiye Health Literacy Scale-32 (THLS-32)

THLS-32 has 32 items and a four-point Likert-type scale. THLS-32 consists of two sub-dimensions, namely treatment and service and disease prevention/health promotion. Higher scores indicate better HL. Scores on the THLS-32 are interpreted as follows: inadequate HL (0-25); problematic/limited HL (>25-33); adequate HL (>33- 42); excellent HL (>42-50). Cronbach's Alfa coefficient is .927 (11). It was found as .965 in the present study.

The Fertility Quality of Life Questionnaire (FertiQoL)

The FertiQol scale includes 36 items and has two modules; core (emotional, mind/body, relational, social) and treatment (environment, tolerability). Scores on the subscales range from 0 to 100. Higher scores indicate better QoL. In the Turkish validity and reliability study of the scale, Cronbach's Alpha coefficient was determined as .905 (12). It was found to be .920 in this study.

Statistical Analysis

Statistical Package for the Social Sciences 24.0 software was used to evaluate the data. Skewness and kurtosis values were determined to vary between ±2, which was thought to show normality. For this reason, parametric tests were used. Independent samples t-test was used to compare two independent groups, and the one-way ANOVA analysis was employed to compare more than two independent groups, and Pearson correlation analysis was utilized to compare two quantitative data. $p \leq .05$ was accepted as the level of statistical significance.

Results

The mean age of participants was 30.81±5.58, the length of marriage was 5.76±4.60 (year) and the count of treatments was 1.93±1.13. Of the participants, 36% had a university education or higher, 67.7% did not have a paid job, 59.1% had a middle level of income, 73.7% had primary infertility, and 39.8% had unexplained infertility (Table 2).

The mean FertiQoL scores of participants were as follows: core FertiQoL, 61.30±19.05; treatment FertiQoL, 62.78±16.76; total FertiQoL, 61.73±16.71. The mean THLS-32 scores of participants were as follows: treatment and service, 36.94±8.66; disease prevention/ health promotion, 35.92±9.57; total THLS-32, 36.46±8.45 (Table 3). Although not given in the table, 7.5% of the participants had inadequate, 28.5% problematic/ limited, 31.7% adequate, and 32.3% excellent health literacy levels.

The mean Treatment and Total FertiQoL scores of participants with a university degree education level were higher than those with a high school education. Participants whose spouses had a university degree education level had higher average Core, Treatment, and Total FertiQoL scores compared to those with primary education. Participants who were employed in income-generating jobs had higher average Core and Total FertiQoL scores than those who were unemployed. Participants with lower monthly income had lower average Core and Total FertiQoL scores compared to those with moderate and high incomes (Table 1; $p<.05$). Participants with secondary infertility had lower average Treatment and FertiQoL scores than those with primary infertility. The Core, Treatment, and Total FertiQoL scores of participants with male-only infertility as the cause were higher than those of participants with infertility due to other reasons (Table 2; $p<.05$).

There was no significant relationship between FertiQoL scores and THLS-32 scores (Table 3; $p>.05$).

Discussion

Infertility and its treatment can affect the women

Table 1. Results of the analysis of the scales according to sociodemographic variables (*n = 186*).

		Core FertiQoL	Treatment FertiQoL	Total FertiQoL	Treatment and services	Disease prevention/ health promotion	Total THLS-32
Variables	***n* (%)**	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Education							
Primary (a)	62 (33.3)	58.42±19.92	62.86±14.60	59.72±16.26	35.289±10.135	33.724±10.918	34.534±9.785
High school (b)	57 (30.6)	59.63±19.17	57.06±18.77	58.88±17.89	37.406±7.754	36.319±9.175	36.921±7.666
University and above (c)	67 (36)	65.38±17.64	67.57±15.49	66.02±15.41	38.077±7.746	37.617±8.211	37.853±7.507
Analysis#		F=2.504 *p*=.085	**F=6.413 *p*=.002* (b-c)**	**F=3.586 *p*=.030* (b-c)**	F=1.804*p*=.168	F=2.791*p*=.064	F=2.650 *p*=.073
Spouse's education							
Primary (a)	45 (24.2)	54.58±21.91	57.22±20.28	55.36±19.63	36.325±10.194	35.637±11.975	35.981±10.400
High school (b)	97 (52.2)	60.91±16.90	63.76±14.80	61.75±14.51	36.887±7.991	35.569±8.485	36.276±7.570
University and above (c)	44 (23.7)	69.01±17.98	66.31±15.86	68.22±15.87	37.694±8.512	36.991±9.211	37.361±8.232
Analysis#		**F=6.829 *p*=.001* (a-c)**	**F=3.721 *p*=.026* (a-c)**	**F=7.010 *p*=.001* (a-c)**	F=.280 *p*=.756	F=.358 *p*=.699	F=.342*p*=.711
Having a paid job							
Yes	60 (32.3)	67.36±17.64	64.00±14.77	66.37±14.67	36.107±7.823	35.487±8.736	35.815±7.572
No	126 (67.7)	58.41±19.08	62.20±17.66	59.52±17.22	37.340±9.028	36.129±9.966	36.769±8.856
Analysis†		**t=3.064 *p*=.003***	t=.727 *p*=.468	**t=2.655 p=.009***	t=-.908 *p*=.365	t=-.426*p*=.670	t=-.719*p*=.473
Monthly income							
Low (a)	61 (32.8)	54.13±20.13	60.45±14.99	55.99±17.15	35.318±9.409	34.598±11.295	35.008±9.447
Middle (b)	110 (59.1)	64.46±17.11	63.93±17.90	64.30±15.63	38.173±7.990	36.532±8.538	37.380±7.726
High (c)	15 (8.1)	67.22±20.95	63.83±14.88	66.23±17.60	34.519±9.157	36.828±9.161	35.632±8.982
Analysis#		**F=6.983 *p*=.001* (a-b; a-c)**	F=.877 *p*=.418	**F=5.723 *p*=.004* (a-b; a-c)**	F=2.830*p*=.062	F=.874 *p*=.419	F=1.634 *p*=.198

Abbreviations: †Independent t-test; **#**One-way ANOVA Test. *p <.05

Table 2. Results of the analysis of the scales according to infertility variables (*n = 186*).

		Core FertiQoL	Treatment FertiQoL	Total FertiQoL	Treatment and services	Disease pre-vention/health promotion	Total THLS-32
Variables	***n* (%)**	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Type of infertility							
Primary	137 (73.7)	61.68±19.26	60.86±16.91	61.44±17.06	37.086±8.478	36.023±9.677	36.596±8.375
Secondary	49 (26.3)	60.23±18.58	68.16±15.26	62.56±15.84	36.540±9.214	35.638±9.349	36.084±8.750
Analysis†		t=457 *p*=.648	**t=-2.661p=.008***	t=-.417 *p*=.688	t=.378*p*=.706	t=.241*p*=.810	t=.363*p*=.717
Cause of infertility							
Female factor (a)	66 (35.5)	62.33±17.69	60.87±16.49	61.90±15.90	36.562±7.607	34.572±8.808	35.563±7.748
Male factor (b)	21 (11.3)	73.61±19.62	70.24±13.69	72.62±16.06	41.468±7.7087	41.353±7.758	41.420±7.443
Both partners (c)	25 (13.4)	56.67±16.23	57.70±15.54	56.97±15.07	34.354±12.3687	33.752±11.003	33.992±11.348
Unexplainable infertility (d)	74 (39.8)	58.45±19.71	64.09±17.58	60.11±17.12	36.871±7.966	36.317±9.732	36.688±7.761
Analysis#		**F=4.248 p=.006* (b-c; b-d)**	**F=2.656 p=.050***	**F=4.077 p=.008* (a-b; b-c; b-d)**	**F=2.782 p=.042* (b-c)**	**F=3.281 *p*=.022* (a-b ; b-c)**	**F=3.524 p=.016* (a-b ; b-c)**

Abbreviations: †Independent t-test; **#**One-way ANOVA Test. *p <.05

Table 3. Correlations between scale scores and various variables

	Mean	SD	1	2	3	4	5	6
Core FertiQoL	61.30	19.05	1	.560**	.970**	.103	.100	.110
Treatment FertiQoL	62.78	16.76		1	.746**	.081	.053	.069
Total FertiQol	61.73	16.71			1	.107	.097	.109
Treatment and services	36.94	8.66				1	.741**	.930**
Disease prevention/health promotion	35.92	9.57					1	.933**
Total THLS-32	36.46	8.45						1

Abbreviations: * *p*<.05; ***p*<.001 (Pearson correlation analyses).

medically, emotionally, psychologically, socially and financially (13). In this study, FertiQoL score was determined as 61.73±16.71 consistent with the literature (14). This result showed that there was a about 40-point decrease in the scale, that is, the treatment negatively affected the quality of life.

The lowest scores were on the emotional and the highest scores were on the relational sub-dimension. This result was similar to the literature (14-16). Infertility causes some psychological problems especially in women, such as emotional stress, depression, anxiety, and low self-esteem (17). Our result is important in terms of showing that emotional problems experienced affect the quality of life. Infertility processes can be easier for patients who can cope with infertility stress. Therefore, nurses and other health professionals should give psychological support to improve patients' emotional states. High scores on the relational sub-dimension suggest that infertile women feel satisfied with their relationships, have strong communication, and believe that fertility problems strengthen their commitment to their relationships.

The course of infertility treatment is a complex process. Patients need information to continue this course more healthily (18). Therefore, infertile individuals must reach the necessary information and understand, evaluate, use, and apply it during infertility and the treatment process. In our study, it was determined that the level of HL was insufficient-problematic/limited in 36% of women and adequate-perfect in 64%. Sahebalzamani et al. found that only 32.1% of infertile women had adequate HL (19). Bennett et al. reported that infertile women had an inadequate level of knowledge about infertility treatment, indicating a general lack of HL in women in terms of describing medical interventions (5). Health literacy plays a crucial role in shaping an individual's health-related actions and their probability of adhering to treatment suggestions (20). Given that the complex process of infertility treatment can impact adherence, enhancing health literacy among infertility patients is crucial.

In this study, the quality of life scores varied according to sociodemographic variables such as education level of the woman and her spouse, employment status in a paid job, and monthly income level. Those with a higher education level had better quality of life. There are studies in the literature showing that higher education level is associated with better quality of life (3, 16, 21). In this study, those employed in paid jobs and those with higher monthly incomes had better quality of life. In the literature, there are studies that support our findings, indicating that employment in a paid job and having a higher economic status are associated with higher quality of life in infertile women (16, 21-23). These results suggest that a higher education level, employment in a paid job, and a high-income level may be associated with having better opportunities that can enhance the quality of life.

In our study, it was determined that the quality of life of women with male factor infertility was higher than other reasons. In a qualitative study, it was determined that problems that infertile women frequently faced were social pressure and stigmatization, they also felt excessive responsibility towards society and their spouses, and that they saw the inability to have children as a burden (24). Infertile women generally had more negative experiences related to infertility in many areas, such as lower self-esteem and physical health, and experienced higher levels of depression, stress, anxiety, stigma, and shame (25). Based on these results, the fact that these symptoms are more common in women explains the low quality of life in those with a female factor as the cause of infertility.

In our study, no relationship was found between the quality of life and number of infertility treatments and the duration of infertility. It can be said that women's quality of life is similarly affected regardless of the duration of infertility and the number of treatments due to the burdens that infertility and the treatment process may bring.

HL has been shown to affect quality of life in different groups (4, 9, 10). To the best of our knowledge, our study is the first to evaluate the relationship between HL and quality of life in infertile women. In our study, it was determined that there is no relationship between the HL of infertile women and their quality of life. Quality of life can be affected by social, psychological, economic and cultural factors (10). It is thought that the quality of life of the women may have been affected by these factors other than HL.

Conclusion

Infertility treatment can be difficult, and disturbing. The women's quality of life in this specific treatment process is important. In this study, it was observed that the quality of life of women who received infertility treatment was not at the desired level. The HL level was inadequate-problematic/limited in 36% of participants and that there was no significant relationship between HL and quality of life. It is recommended that nurses, and other health professionals in the team should plan interventions to improve quality of life and HL during the infertility treatment.

Limitations

This study has several limitations. Firstly, the data were collected from a single center, limiting the generalizability of the findings to the broader population of infertile women. Secondly, our study included infertile women while excluding their spouses from the scope of the research.

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Author contributions: MNA: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft. FÖ: Supervision, Conceptualization, Investigation, Methodology, Project administration, Writing – original draft.

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ORIGINAL ARTICLE

Parents' Knowledge Level About New Food Fear and Food Allergies

Ebeveynlerin Yeni Besin Korkusu ve Besin Alerjileri Konusunda Bilgi Düzeyi

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ABSTRACT

Aim: This study aimed to investigate the prevalence of food neophobia among parents of primary school-aged children, identify common allergenic foods in children, and assess parents' knowledge about food allergies.
Material and Methods: A descriptive cross-sectional study was carried out with parents of students attending public primary schools in a district of the Central Anatolia region in Türkiye during the spring semester of the 2022-2023 academic year. The study was conducted with 341 parents of students selected by a simple random sampling method. Data were collected using a survey method, including a researcher-prepared data collection form and the 'Fear of New Food Scale.' Data were analyzed using the Kruskal-Wallis and Mann-Whitney U tests. Pearson correlation analysis was utilized for examining correlation relationships.
Results: The majority of parents displayed moderate food neophobia (85.4%), with milk and dairy products, eggs, strawberries and dyed sugar and chocolate being the most frequently reported allergenic foods for children. A significant proportion of parents (54.8%) lacked information about food allergies. The study reveals that as parents' knowledge of food allergy symptoms and prevention of allergic reactions increases, their burden as measured by the FNS score tends to decrease.
Conclusion: These findings have noteworthy implications for pediatric nursing practice, emphasizing the necessity for targeted interventions to educate parents about food allergies and promote safe practices in managing allergic reactions.

Keywords: Allergens, child, food neophobia, parents, primary school.

ÖZ

Amaç: Bu çalışmanın amacı, ilkokul çağındaki çocukların ebeveynleri arasında gıda neofobisinin yaygınlığını araştırmak, çocuklarda yaygın alerjen gıdaları belirlemek ve ebeveynlerin gıda alerjileri hakkındaki bilgilerini değerlendirmektir.
Gereç ve Yöntemler: Tanımlayıcı kesitsel bir çalışma, 2022-2023 eğitim-öğretim yılı bahar döneminde Türkiye'nin İç Anadolu bölgesindeki bir ilçede bulunan devlet ilkokullarına devam eden öğrencilerin ebeveynleri ile gerçekleştirilmiştir. Çalışma, basit tesadüfi örnekleme yöntemiyle seçilen 341 öğrenci velisi ile yürütülmüştür. Veriler, araştırmacı tarafından hazırlanan veri toplama formu ve 'Yeni Besin Korkusu Ölçeği'ni içeren bir anket yöntemi kullanılarak toplanmıştır. Veriler Kruskal-Wallis ve Mann-Whitney U testleri kullanılarak analiz edilmiştir. Korelasyon ilişkilerini incelemek için Pearson korelasyon analizi kullanılmıştır.
Bulgular: Ebeveynlerin çoğunluğu (%85,4) orta düzeyde gıda neofobisi sergilerken, süt ve süt ürünleri, yumurta, çilek ve boyalı şeker ve çikolata çocuklar için en sık bildirilen alerjen gıdalar olmuştur. Ebeveynlerin önemli bir kısmı (%54,8) gıda alerjileri hakkında bilgi sahibi değildir. Çalışma, ebeveynlerin gıda alerjisi semptomları ve alerjik reaksiyonların önlenmesi konusundaki bilgileri arttıkça, FNS skoru ile ölçülen yüklerinin azalma eğiliminde olduğunu ortaya koymaktadır.
Sonuç: Bu bulgular, ebeveynleri gıda alerjileri konusunda eğitmek ve alerjik reaksiyonları yönetmede güvenli uygulamaları teşvik etmek için hedeflenen müdahalelerin gerekliliğini vurgulayarak, pediatrik hemşirelik uygulamaları için kayda değer çıkarımlara sahiptir.

Anahtar Kelimeler: Alerjenler, çocuk, gıda neofobisi, ebeveynler, ilkokul.

Introduction

Food allergies pose a significant health concern, capable of triggering life-threatening reactions and impacting the well-being of both patients and their loved ones. Among allergic conditions prevalent in childhood, food allergies hold a prominent position (1).It affects approximately 10% of the pediatric population (2). Food allergies manifest as an abnormal immune system response to ingested food proteins (3). Even a small ingestion of allergenic food can lead to a diverse range of symptoms, ranging from mild manifestations like hives and gastrointestinal discomfort to severe anaphylaxis. Primary risk factors for food allergies include atopic dermatitis, asthma, and a family history of atopy. While there are around 170 identified allergenic foods, only a select few foods account for the majority of reactions (4). The specific allergenic foods commonly associated with allergic reactions in children may vary based on geographical location and individual sensitivities (3). However, some frequently reported allergenic foods in children include milk, eggs, peanuts, soy, wheat, fish, and shellfish. Notably, milk, egg, wheat, and soy allergies typically manifest during childhood, whereas peanut, nut, and seafood allergies can occur at any stage of life (5). Allergies to commonly consumed foods such as milk, eggs, wheat, and soy predominantly arise during childhood while allergies to peanuts, nuts, and seafood can manifest at any stage of life. It is worth noting that although fruits and vegetables are generally regarded as healthy and beneficial, some children may develop allergies

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to specific varieties. Notably, less common allergenic fruits and vegetables that can trigger allergies in children include kiwi, banana, strawberry, avocado and tomato (6-7). Effective management of food allergies revolves around the meticulous avoidance of known allergenic foods and ensuring continuous access to life-saving epinephrine. The European Academy of Allergy and Clinical Immunology offers recommendations to prevent the onset of sudden food allergies in infants and young children (8). Given that milk, egg, wheat, and soy allergies often manifest during childhood, it is not uncommon for schools to have at least one student with a food allergy. While no specific studies have assessed the frequency of allergic reactions in schools within our country, research conducted in the United States revealed that at least one anaphylactic reaction occurred in 10% of 5,683 schools during the 2013–2014 academic year. Furthermore, approximately 18% of children with food allergies experienced at least one allergic reaction during their school years (9).Notably, a quarter of allergic reactions in schools were the first-time occurrence in children (U.S. Study, personal communication). One-quarter of allergic reactions in schools are first-time allergic reactions in children (9-10).

Indeed, it is believed that parents of children with food allergies often experience a heightened sense of apprehension towards foods available outside their homes. As a result, parents bear the weight of managing food allergies, which can cultivate fear and anxiety towards unfamiliar foods (11-12). In addition to established food allergies, parents' knowledge about new food fears is also important to consider. As new foods are introduced into a child's diet, there may be concerns about potential allergic reactions or adverse effects (13). It is essential to acknowledge that parents' level of knowledge about new food fears, such as concerns about food intolerances, sensitivities, or unfamiliar ingredients, can also impact their ability to make informed decisions about their child's diet (14). By addressing both food allergies and new food fears, healthcare professionals can provide comprehensive support and education to parents, ensuring the well-being and safety of their children. Understanding the attitudes surrounding food allergies is crucial to raising awareness and providing education to parents on this matter. The task of managing food allergies can prove particularly challenging for parents with primary school-aged children. Not only must they ensure the safety of their children, but they must also navigate social and school environments where allergens may be present.

When the literature is reviewed, the studies conducted by Hörold et al. (2023), Lim & Law (2023), Doğan et al. (2023), and Cardosa et al. (2023) primarily focus on parents' information needs, behavioral pursuits, fears and awareness about the prevention and management of food allergies in children (13-16). These studies shed light on different aspects of parents' experiences and concerns about food allergies. While previous studies have provided valuable information about parents' information needs, fears, and awareness of food allergies, the current study differs by focusing specifically on parents of primary school-aged children and assessing their knowledge about food allergies and their concerns when introducing new foods. This study aims to complement the existing literature on parents' experiences and needs in the prevention and management of food allergies in children.

Research questions

1. How do parents' fear levels about food allergies vary according to demographic factors?

2. What are parents' levels of the Food Neophobia Scale?

3. How is parents' knowledge about food allergies related to their level of concern about introducing novel foods to their children?

Methods

Study design

A descriptive cross-sectional study was used for this research.

Study location and duration

The study was conducted in a district in the Central Anatolia Region of Türkiye, specifically targeting parents of students enrolled in primary schools in the spring semester of the 2022–2023 academic year. Data collection was conducted through a survey between March 20 and June 2023.

Population and sample of the study

The target population for this study comprised four primary schools in a district of the Central Anatolia region in Türkiye, which collectively accommodated 2,600 students receiving official primary school education. The sample selection was based on the use of simple random sampling. This method was chosen to ensure that each member of the population, specifically the parents of primary school students, had an equal opportunity to be included in the sample. By employing this sampling technique, the researchers aimed to gather information that could be generalized to a larger population of parents within the district. To provide further context, the population consisted of 2,600 students aged between 7 and 10 years, enrolled in the 1st, 2nd, 3rd, and 4th grades across four selected primary schools. These schools were chosen through a simple random sampling method from a pool of 10 general primary schools located in the district center. The decision to focus on parents with children in these specific grade levels is a common practice in research studies. The initial sample size for this study was determined as 335 parents of students, based on a power analysis that considered a 95% confidence interval, 95% population representation, and an alpha level of 0.5%. G*Power 3.1.9.7. was used to calculate the minimum sample size to analyze. However, the actual number of participants in the study exceeded

this initial sample size, totaling 361 parents. These individuals were selected based on meeting the inclusion criteria and willingly agreeing to participate during the designated data collection period, following the acquisition of necessary permissions. The decision to include additional participants beyond the initial sample size of 335 was driven by factors such as enhancing statistical power and minimizing potential data loss. The inclusion criteria entailed being parents of primary school students and voluntary participation in the survey. Participants who declined to take part in the study for various reasons, such as time constraints, were excluded from the study, ensuring that only willing participants were included in the final sample. During the data collection process, 20 people participated in the survey, but they were not included in the analysis because they did not answer some questions in the data collection form. The study was completed with 341 participants.

Data collection tools

The data for this study were gathered through the utilization of two main data collection tools: a data collection form developed by the researcher and the 'New Food Fear Scale'. The study data were collected by the survey method. The duration of the survey was set to last 10–15 minutes.

Data collection form

The data collection form consisted of 15 carefully crafted questions that encompassed various aspects (11,14-16). These questions covered sociodemographic characteristics such as age, gender, family type, income level, parental education, parental occupation, and number of siblings. Additionally, the form included inquiries concerning information related to food allergies, including the child's food allergy status, duration of diagnosis, and any symptoms experienced by the parents due to food allergies. The form also inquired about the solutions and preventive measures taken by the parents to manage food allergies.

The New Food Fear (Food Neophobia) Scale

The Food Neophobia Scale (FNS), originally named "Food Neophobia Scale", was developed by Pliner and Hobden to examine the neophobic (fear of new foods) and neophilic (liking of new foods) states in humans, specifically to enable the measurement of fear of new foods with paper and pencil and to examine the relationships between fear of new foods assessed with this scale (17). The Turkish validity and reliability study of the scale was conducted by Uçar (18). The 7-point Likert-type scale consisting of ten items is organized in such a way that 1 point increases for each option from strongly disagree (1 point) to strongly agree (7 points). It ranges from 10-70 points (questions 1, 4, 6, 9, and 10 are reverse-scored). As the score obtained from the scale increases, the level of food neophobia increases. The adaptation of the FNS scale into Turkish for use in our country was studied by Uçar as a master's thesis in 2018 and published as a scale in 2021 (18-19).The scale adapted into Turkish by Uçar was used with the permission of the researcher. The Cronchbach alpha coefficient of the scale is 0.80. The Cronchbach alpha coefficient was 0.64 in our study. In this study, the FNS quartiles obtained from the participants were determined, and the scoring of the scale was determined as follows:

Between 10-33 points: neophilic group (negative attitude towards new foods)

Between 34 and 47 points: neutral group (group in the middle)

48–70 points: neophobic group (fear of new foods).

Collection of data

For this study, data collection was conducted utilizing a data collection form and a new food fear scale. The primary objectives were to ascertain the prevalence of food allergies among primary school children and to investigate the level of knowledge of parents about fear of new foods. Only participants who voluntarily agreed to take part in the study were included. To administer the questionnaire forms, the researchers reached out to the principals and teachers of primary school educational institutions within the district. Subsequently, the questionnaire forms were distributed by hand to the parents of the students. Prior to participation, comprehensive information about the study was provided to the parents, along with an informed consent form. This ensured that participants were well-informed and gave their explicit consent to be involved in the study. Using this methodological approach, the researchers aimed to collect reliable and understandable data about food allergies and parents' fear of new foods in the context of primary school children.

Data analysis

The data obtained from the study were evaluated on a computer using the SPSS 22.0 (Statistical Package for Social Sciences) program. Number and percentage distributions were used as descriptive statistics. Mean, standard deviation, minimum and maximum values were calculated for quantitative data. The Shapiro-Wilk-Wilk was applied for the normality test, and Kruskal-Wallis and Mann-Whitney U tests were used for non-normally distributed data. Pearson correlation analysis was utilized for examining correlation relationships. $p<0.05$ was considered statistically significant.

Ethical aspects of the research

Permissions were obtained from Selcuk University Faculty of Medicine Local Ethics Committee (29.03.2023-E.480855, 2023/152), Konya Provincial Directorate of National Education (11.04.2023, E-83688308-605.99-74212673), and parents who agreed to participate in the study.

Results

Table 1 shows that the mean age of the children was 8.73 ± 0.97 years. It was found that 84.5% of the parents who participated in the study were the mothers of

Table 1. Mean scores of the FNS according to the socio-demographic characteristics of the parents who participated in the study (N = 341).

				FNS Total Score
Socio-demographic characteristics		n	%	Median [IQR]
Parent of the child	Mother	288	84.5	41.0 (7.75)
	Father	53	15.5	42.0 (7.50)
p	0.496*			
Gender of the child	Girl	203	59.5	40.0 (6.0)
p	Boy 0.010*	138	40.5	42.0 (10.0)
Family type	Nuclear family	285	83.6	41.0 (9.0)
	Extended family	52	15.2	43.0 (3.0)
	Fragmented family	4	1.2	39.0 (9.0)
p	0.477**			
Income level	Income less than expenditure[1]	91	26.7	40.0 (9.0)
	Income equals expenditure [2]	188	55.1	41.5 (5.0)
	Income more than expenditure[3]	62	18.2	37.5 (8.0)
p	0.001** 2>3			
Mother's education	Literate[1]	2	0.6	41.5 (7.0)
	Primary school[2]	59	17.3	42.0 (5.0)
	Middle school[3]	73	21.4	44.0 (7.0)
	High school[4]	135	39.6	40.0 (7.0)
	Associate[5]	26	7.6	47.0 (3.0)
	License[6]	40	11.7	39.0 (7.0)
p	Master-Doctorate[7] 0.001 ** 5>3>2>1>4>6>7	6	1.8	36.0 (0.0)
Father's education	Literate[1]	-	-	-
	Primary school[2]	21	6.2	42.0 (1.50)
	Middle school[3]	85	24.9	40.0 (11.0)
	High school[4]	113	33.1	40.0 (5.50)
	Associate[5]	57	16.7	43.0 (8.0)
	License[6]	45	13.2	43.0 (5.50)
p	Master-Doctorate[7] 0.001 ** 5=6>2>3=4>7	20	5.9	36.0 (0.00)
Mother occupation	Civil servant[1]	46	13.5	37.0 (7.0)
	Worker[2]	10	2.9	41.0 (14.75)
	Self-employment[3]	42	12.3	41.0 (2.25)
	Retired[4]	-	-	-
p	Not working[5] 0.011 ** 5=3=2>1	243	71.3	41.0 (9.0)
Father occupation	Civil servant[1]	74	21.7	41.5 (9.0)
	Worker[2]	126	37.0	42.0 (5.0)
	Self-employment[3]	122	35.8	41.0 (7.25)
	Retired[4]	9	2.6	40.0 (16.0)
p	Not working[5] 0.011 ** 5=3=2>1	10	2.9	45.0 (3)
Number of siblings	Only child[1]	33	9.7	36.0 (5.50)
	A sibling[2]	127	37.2	41.0 (9.0)
	Two siblings[3]	110	32.3	42.5 (7.25)
p	Three siblings and above[4] 0.002 ** 3>1	71	20.8	40.0 (7.0)
Age of child		**Mean±Sd** 8.73± 0.97		

*Mann Whitney U test, **Kruskal Wallis test. FNS: Food Neophobia Scale.

Table 2. Parents' New Food Fear Scale Scores

Quartiles	FNS Score	n	%
Neophilic (Low)	10-33	16	4.7
Neutral (Moderate)	34-47	292	85.4
Neophobic (High)	48-70	33	9.9
Total	10-70	341	100.0

FNS: Food Neophobia Scale. n: number. %: percentage.

Table 3. Parents' knowledge about food allergy

Features related to food allergy		n	%
Child's food allergy status	Yes	49	14.4
	No	292	85.6
Foods that children with food allergies are allergic to	Milk and dairy products	14	28.6
	Eggs	11	22.4
	Wheat	1	2.0
	Lentil	1	2.0
	Peanuts	3	6.1
	Tomato	1	2.0
	Strawberry	8	16.3
	Fish	2	4.1
	Bal	1	2.0
	Food-dyed candy and chocolate	7	14.3
Number of days since diagnosis for children with food allergy	1-6 months	7	14.3
	7-12 months	12	24.5
	13-23 months	4	8.2
	24 months and above	26	53.1
Parental knowledge of food allergy symptoms	Hives and very itchy raised skin patches	58	17.0
	Red swollen skin	32	9.4
	Itchy watery or swollen eyes	23	6.7
	Runny nose and sneezing	26	7.6
	Throat swelling	15	4.4
	Wheezing, coughing a lot, difficulty breathing	68	19.9
	Vomiting and diarrhea	31	9.1
	I don't know	88	25.8
Parents' knowledge on food allergy testing	Diagnosed by skin test	40	11.7
	Diagnosed with a blood test	39	11.4
	Diagnosed with both skin and blood tests	75	22.0
	I don't know	187	54.8
The solution parents turn to when their children develop food allergies	I'll call an ambulance	113	33.1
	I'll take him/her to the hospital myself	212	62.2
	I keep an epinephrine syringe with me and administer it to the child in case of allergy	5	1.5
	Do nothing, wait for the allergy reaction to pass	11	3.2
Knowledge of the prevention of allergic reactions in the child	Yes	293	85.9
	No	48	14.1
Solutions for parents to prevent a possible allergic reaction in the child	I read food labels and try to keep my child away from allergenic foods	279	81.8
	If we are going to eat out, I inform the person preparing the food about the food my child is allergic to	45	13.2
	I adorn my child's arm with an informative bracelet that imparts knowledge about the specific foods to which my child is allergic	17	5.0

n:number. %: percentage.

Table 4. Correlation relationship between parents' knowledge about food allergies and the FNS Total Score

	FNS Total Score	
	r	p
Parental knowledge of food allergy symptoms	-0.160*	0.003
Parents' knowledge on food allergy testing	0.008	0.879
Knowledge of the prevention of allergic reactions in the child	-0.109*	0.045

***** Pearson Correlation analysis. Correlation is significant at the 0.02 level (2- tailed).

the children, 83.6% of them lived in a nuclear family, and 55.1% of them had an income equal to their expenses. It was also found that families with male children had more fear of new foods. Families with equal income levels had higher levels of fear of new foods than families with higher income levels. It was determined that the significant difference between mothers' education levels was caused by mothers with associate degree education. The significant difference between the father's education level was caused by the father's associate degree education level. Non-working mothers had a higher level of fear of new foods than civil servant mothers. Non-working fathers had a higher level of fear of new foods than retired fathers. Families with three children had higher levels of fear of new foods than families with one child.

According to the fear of novel food scale scores, 4.7% of the participants were neophilic, 85.4% were neutral, and 9.9% were neophobic. The mean FNS score was 41.21±6.11 (Table 2).

In the study, 85.6% of the children did not have a food allergy. Among those with food allergies, 28.6% were allergic to milk and dairy products, 22.4% to eggs, 16.3% to strawberries, and 14.3% to food-dyed sugar and chocolate. When asked about the number of days since the diagnosis of food allergies, 53.1% responded that it had been 24 months or more. When parents were asked about their knowledge of symptoms of food allergies, 25.8% said they had no knowledge, 19.9% said they had symptoms such as wheezing, coughing a lot, and difficulty breathing, and 17.0% said they had symptoms such as hives and very itchy skin spots. 54.8% of the parents reported that they had no knowledge about food allergies, and 22.0% reported that they could be diagnosed by both skin and blood tests. Among the solution that parents would use when their children had food allergies, 62.2% said that they would take the child to the hospital immediately, and 33.1% said that they would call an ambulance. 85.9% of parents think that allergic reactions caused by food allergies can be prevented. To prevent a possible food allergic reaction in a child, 81.8% of the parents reported that they read food labels and kept their child away from allergenic foods (Table 3).

The correlation between parents' knowledge of their children's food allergy symptoms, allergy testing, how to prevent allergic reactions, and FNS scores is shown in Table 4. There is a statistically significant but weak negative correlation between parental knowledge of food allergy symptoms and the FNS total score. The negative correlation indicates that as parental knowledge about food allergy symptoms increases, the FNS score tends to decrease. In other words, parents with higher levels of knowledge about food allergy symptoms tend to experience a lower burden related to their children's food allergies. There appears to be a statistically significant but weak negative relationship between parents' knowledge about preventing allergic reactions in their children and the FNS total score. A negative correlation indicates that FNS scores tend to decrease as parents' knowledge about preventing allergic reactions in their children increases. In other words, parents who have a higher level of knowledge about preventing allergic reactions may experience less burden regarding their children's food allergies.

Discussion

Food allergies have become a growing global concern, affecting individuals of all ages. Among the population, children are particularly susceptible to food allergies, placing parents in a pivotal role when it comes to managing and addressing these allergies (8). To develop effective strategies that support children with food allergies and ensure their safety in both school and home environments, it is crucial to comprehend parents' attitudes towards food allergies and their levels of fear towards unfamiliar foods (1).

This study endeavors to investigate the attitudes of parents with primary school-aged children towards food allergies as well as their experiences with fear of novel foods. The concerns surrounding food allergies can significantly impact the daily lives of parents and their children, influencing dietary choices, social interactions and overall quality of life (20).Parents' attitudes towards food allergies and their associated fears hold great influence over the management and prevention of allergic reactions. A positive and well-informed attitude can prompt proactive measures, including the implementation of appropriate dietary restrictions, education of caregivers and school personnel, and ensuring access to emergency medications. Conversely, negative attitudes or heightened levels of fear can lead to excessive restrictions, social isolation and unnecessary anxiety for both parents and children (21).

The FNS, according to the socio-demographic characteristics of the parents

Parental food neophobia can be influenced by various sociodemographic characteristics, as discovered in the study conducted by Torres et al. (2020) (22). The findings of this study indicate that families with male children tend to exhibit higher levels of fear towards unfamiliar foods, thereby shedding light on a potential gender-related disparity in parental attitudes towards food allergies and the introduction of novel foods.Unfortunately, there is a scarcity of studies in the literature specifically addressing this observation. In a qualitative study by Gallarger et al. (2012), a mother of a 13-year-old boy expressed deep concern and fear regarding her child's food allergies (23). Similarly, another study revealed that some adolescents with peanut allergies found it disconcerting that their parents worried about them and sought to exert control over their lives (24). Unlike the study, in 2023 Białek-Dratwa & Kowalski found that the risk of nutritional problems, including food neophobia, was not associated with age or gender in Polish children (25). These studies collectively highlight that parents tend to experience food fears related to allergies and express worries about their children's well-being (26-27). The implications of these findings

may suggest that families with male children exhibit greater concerns compared to families with female children. Consequently, parents may approach new experiences, including trying unfamiliar foods, with heightened caution.

In the study, it was observed that the level of fear towards new foods tends to increase in parents with equal income levels, those with an associate's degree education whether they are employed or not, and those with multiple children. It is worth noting that the impact of demographic factors may vary across studies. Contrary to our findings, some studies have reported higher food neophobia among individuals with lower levels of education (28) while similar to our study, higher levels of neophobia have been observed among individuals with higher levels of education (29). Several studies have emphasized the significant role parents play in shaping children's eating habits (30-32). Furthermore, it has been highlighted that food allergies can instill anxiety in parents, consequently influencing the child's nutrition and care (33). Children's eating behaviors are greatly influenced by the behaviors and reactions of those around them as they observe and imitate these actions. Moreover, studies have found a correlation between higher levels of neophobia in mothers and the highest levels of neophobia in children (34). Therefore, reinforcing healthy eating habits during childhood becomes a crucial strategy for reducing parental food neophobia. Additionally, parents themselves are expected to maintain adequate eating habits as well.

Parents' New Food Fear Levels

In the study, the majority of parents (85.4%) were classified under the neutral category, indicating a moderate level of food neophobia. These individuals exhibit a balanced stance towards new foods, neither strongly embracing nor strongly avoiding them. They generally display openness to trying unfamiliar foods albeit with a hint of hesitation or caution when confronted with unfamiliar food choices. Previous studies have also yielded similar findings, highlighting the varying levels of neophobia experienced by parents (18, 22, 28, 35).

Parents' knowledge about food allergies

The study reveals a potential knowledge gap among parents regarding food allergies, with a significant proportion (54.8%) expressing a lack of understanding. However, there is evidence that a notable percentage (22.0%) of parents are familiar with diagnostic approaches such as skin and blood tests for food allergies. In terms of intervention strategies, the majority of parents (62.2%) indicated their proactive approach of seeking medical attention promptly at a hospital, while a significant percentage (33.1%) acknowledged the need to contact emergency services for immediate assistance. This highlights the importance of timely medical intervention in managing food allergy emergencies. A substantial majority of parents (85.9%) expressed belief in the preventability of allergic reactions caused by food allergies, demonstrating a willingness to adopt preventive measures. Additionally, a significant proportion (81.8%) reported actively reading food labels and ensuring their children avoid allergenic foods, indicating proactive efforts to mitigate the risk of allergic reactions. These findings emphasize the crucial role of parental engagement in establishing a safe food environment for children with food allergies. It is worth noting that existing literature also highlights the significance of providing parents with education on food allergy management and the importance of adopting a multidisciplinary approach involving healthcare professionals to address new food fears (30, 32, 34). Such efforts aim to enhance parental knowledge and equip them with the necessary skills to effectively navigate the challenges associated with food allergies.

Correlation relationship between parents' knowledge about food allergies and the FNS Total Score

The study reveals that as parents' knowledge of food allergy symptoms and prevention of allergic reactions increases, their burden measured by the FNS score tends to decrease. This suggests that parents with higher levels of knowledge experience a lower burden when managing their children's food allergies. The findings are in line with previous literature highlighting the positive impact of parental knowledge on reducing burden and improving the management of food allergies in children, including studies by Hörold et al. (2023), Lim et al. (2023), and Cardoso et al. (2023) (13-14, 16). These studies emphasize the importance of providing comprehensive information and addressing parents' information-seeking behaviors and needs to improve their ability to effectively prevent and manage food allergies.

Limitations

The research is a cross-sectional study and is limited to the verbal statements of the participants. Data was collected by the survey method. The use of a single scale in the study and not using another scale limits the study.

Implications for practice

These findings underscore the importance of pediatric nurses in providing valuable education to parents, promoting strategies for allergen avoidance, and supporting effective management of food allergies. By implementing evidence-based recommendations, nurses can empower parents to ensure the safety and well-being of their children who are affected by food allergies. Nurses play a crucial role in educating parents about new food fears and food allergies. They should assess parents' knowledge levels, provide accurate information, clarify misconceptions, teach avoidance strategies, demonstrate emergency response, collaborate with other healthcare professionals, offer emotional support and promote community resources. By doing so, nurses empower parents to effectively manage their children's food allergies and ensure their overall well-being. Moving forward, future research should focus on evaluating

the effectiveness of educational interventions and developing standardized protocols for pediatric nursing practice in the management of food allergies. This will contribute to enhancing the quality of care and support provided to children and their families facing the challenges of food allergies.

Conclusion

In conclusion, the findings of the study shed light on several important aspects. Firstly, it revealed that the majority of parents displayed a moderate level of food neophobia (85.4%), indicating a balanced inclination towards trying new foods. The study also identified the most common allergenic foods in children, which included milk and dairy products, eggs, and strawberries, as well as food dyed sugar and chocolate. Furthermore, the study uncovered a significant knowledge gap among parents, with 54.8% reporting a lack of awareness about food allergies. This highlights the need for targeted education and information dissemination to bridge this crucial gap in parental understanding. Raising awareness of food allergies and addressing new levels of food fear among parents of primary school-aged children requires a multifaceted approach combining political and economic measures. Policymakers and stakeholders can create a safer and more inclusive environment for children with food allergies by implementing the following recommendations:

Governments should invest in educational programs targeting parents, teachers, school staff, and healthcare professionals to improve their understanding of food allergies. This would involve providing education on symptom recognition, emergency response procedures, and the importance of allergen avoidance. Strict regulations on allergen labeling for packaged foods should also be imposed, ensuring clear and standardized labeling that includes common allergens and cross-contamination risks. Additionally, governments should try to make epinephrine auto-injectors more accessible and affordable. Schools should develop comprehensive food allergy management policies, collaborating with relevant stakeholders to create allergen-free meal options, safe food handling practices, and individualized allergy management plans. Lastly, stakeholders should collaborate to raise awareness, share information, and advocate for the needs of children with food allergies. By implementing these measures, society can better support children with food allergies. Increased awareness, education, and support will create an environment where these children can thrive, ensuring their safety, participation, and overall well-being.

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ORIGINAL ARTICLE

The Impact of the COVID-19 Pandemic on the Stress Levels of Pregnant Women

COVID-19 Salgınının Gebelerin Stres Düzeylerine Etkisi

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ABSTRACT

Aim: This study aims to determine the effects of the COVID-19 process on pregnant women in the second and third trimesters, as well as the stress they have experienced and their health behaviors.
Material and Methods: The research is of descriptive cross-sectional type. The sample size was calculated using the G*Power program. Necessary permissions were obtained for the research. Due to restrictions in the data collection time period (November 2020-April 2021), 204 participants were reached by convenience sampling method using the online survey tool. A survey form consisting of three parts was used as a data collection tool. Personal information form including questions about sociodemographic characteristics, birth history, pregnancy and pandemic; Pregnancy Stress Rating Scale and Coronavirus Anxiety Scale were employed. High scores on the Pregnancy Stress Rating Scale indicate an increased level of stress during pregnancy. A high score on the Coronavirus Anxiety Scale indicates a high level of anxiety experienced during the coronavirus. In the study, number and percentage values were given, regression and correlation analysis and nonparametric tests were performed.
Results: It was found that pregnant women experienced moderate stress during the COVID-19 pandemic, and some obstetric characteristics such as gestational week, having problems in this and previous pregnancies, feeling fear of delivery, and having problems in previous delivery affected stress and COVID-19 anxiety. It has been observed that future anxiety increases in pregnant women who consider the measures taken as inadequate. The mean scores of the scales used in the study are 42.99 ± 24.58 (Min-max: 6-116, median: 40) for Pregnancy Stress Rating Scale, 2.60±3.26 (Min-max: 0-19, median: 2) for Coronavirus Anxiety Scale.
Conclusion: The COVID-19 pandemic is one of the factors contributing to increased stress and anxiety in pregnant women.

Keywords: Anxiety, COVID-19, pandemic, pregnant woman, stress.

ÖZ

Amaç: Bu çalışma, COVID-19 sürecinin ikinci ve üçüncü trimesterdeki gebeler üzerindeki etkilerinin yanı sıra yaşadıkları stres ve sağlık davranışlarının belirlenmesini amaçlamaktadır.
Materyal ve Metod: Araştırma, tanımlayıcı kesitsel tiptedir. Örneklem büyüklüğü G*Power programı kullanılarak hesaplanmıştır. Araştırma için gerekli izinler alınmıştır. Veri toplama zaman dilimindeki (Kasım 2020-Nisan 2021) kısıtlamalar nedeniyle çevrimiçi anket aracı kullanılarak kolayda örnekleme yöntemiyle 204 katılımcıya ulaşılmıştır. Veri toplama aracı olarak üç bölümden oluşan anket formu kullanılmıştır. Sosyodemografik özellikler, doğum öyküsü, gebelik ve pandemiye ilişkin soruların yer aldığı kişisel bilgi formu, Gebelik Stres Derecelendirme Ölçeği ve Coronavirüs Kaygı Ölçeği. Gebelik Stres Derecelendirme Ölçeğinde yüksek puanlar gebelik sırasında artan stres düzeyini göstermektedir. Coronavirüs Kaygı Ölçeği puanının yüksek olması ise koronavirüste yaşanan kaygı düzeyinin fazla olduğunu göstermektedir. Araştırmada sayı ve yüzde değerleri verilmiş, regresyon ve korelasyon analizi ile nonparametrik testler yapılmıştır.
Bulgular: Gebelerin COVID-19 salgını sırasında orta düzeyde stres yaşadıkları ve gebelik haftası, bu gebeliğinde ve önceki gebeliğinde sorun yaşamış olma, doğuma yönelik korku hissetme, önceki doğumunda sorun yaşamış olma gibi bazı obstetrik özelliklerin stres ve COVID-19 kaygısını etkilediği saptanmıştır. Alınan önlemleri yetersiz gören gebelerde gelecek kaygısının arttığı görülmüştür. Çalışmada kullanılan ölçeklerin ortalama puanları Gebelik Stresini Değerlendirme Ölçeği için 42,99 ± 24,58 (Min-max: 6-116, medyan: 40), Koronavirüs Anksiyete Ölçeği için 2,60 ± 3,26 (Min-max: 0-19, medyan: 2) olarak belirlenmiştir.
Sonuç: COVID-19 salgını gebe kadınlarda stres ve kaygı düzeyinin artmasında etkili faktörlerden biridir.

Anahtar Kelimeler: Anksiyete, COVID-19, pandemi, gebe kadın, stres.

Introduction

While the pandemic COVID-19 outbreak resulted in abrupt/unanticipated changes in the medical infrastructure's functioning (1), the literature indicates that epidemics are particularly dangerous for pregnant women, who face a higher mortality risk than the general population (2). Pregnancy is a rewarding yet challenging period of life that requires physical, psychological, and social adaptation as pregnant women often tend to experience anxiety. The global impact of the COVID-19 pandemic in 2019 has necessitated a revaluation of various aspects for pregnant women (3). For instance, a challenge had been the lack of consistent and verified information regarding the effects of the pandemic on pregnancy during its early stages. Studies showed that pregnant women during this period generally tended to experience higher levels of anxiety and emotional distress, particularly in the first trimester, compared to their counterparts in

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later stages of pregnancy (4). Some research has also suggested that higher education might be a risk factor for elevated anxiety levels in pregnant individuals (5). According to research conducted in Italy during the early period of COVID-19, pregnant women described the pandemic's psychological impact as "severe," with more than two-thirds reported feeling "anxious" (6). Numerous studies conducted in various countries concluded that pregnant women were impacted by this condition, exhibited depressive symptoms, and suffered from anxiety disorders (3, 7-11). The fact that the COVID-19 virus showed mutational properties and that epidemics remained with global fluctuations also affected the clinical process of the pregnancy and the emotional states of pregnant women during the process. Many factors such as isolation, decrease in social support, disturbance of routines, and misinformation affect pregnant women's well-being (6).

The COVID-19 pandemic is important in terms of emotional reactions such as anxiety, distress, and fear, all of which negatively impact pregnant women. According to the literature, pregnant women are concerned about their own and their infant's health as a result of the pandemic. Their expectations for antenatal care have deteriorated; they lack reliable information, and their daily routines and social interactions have lessened (12).

This study aims to determine the effects of the COVID-19 process on pregnant women in the second and third trimesters, as well as the stress they experienced and their health behaviors.

Material and Methods

Survey type

The present quantitative and descriptive cross-sectional study utilized a general survey model. Due to the globalization of the epidemic and the restriction of close contact associated with social isolation, data were obtained via an online survey between November 2020 and April 2021 on the internet environment. Google surveys were used for this purpose. The participants were included in the study on a voluntary basis. The information text attached to the survey mentioned the purpose of the research, and access to the questions was provided to those who voluntarily agreed to participate in the study. The survey links were sent to participants through social media platforms.

Population and Sample of the Study

The G*Power 3.1 program was used to calculate the sample size [effect size = 0.20, 1-β = 0.80, α = 0.05]. The effect size was taken as 0.20 in line with Cohen's reference intervals (13). It was determined that a minimum of 199 pregnant women should be included in the sampling, and the study was concluded with 204 participants. The study consists of pregnant women in the second and third trimesters who stated that they had not been diagnosed with any psychiatric disorder. The data were collected through non-probability and convenience sampling methods.

Data Collection Tools

The questionnaire form consists of three parts.

Personal Information Form: It includes questions about sociodemographic characteristics, obstetric history, pregnancy, and pandemic (4,5,10,14,31).

Pregnancy Stress Rating Scale (PSRS): The items in the scale are positive and graded with a five-point Likert type. While the answer "absolutely no" is scored as 0 point, "very severe" is scored as 4 points. The total score is the prenatal stress score. The minimum score that could be obtained from the scale was 0, and the maximum score was 144. A higher score indicates a higher perceived level of prenatal stress. The scale, originally developed in 1983 by Chen and his colleagues, initially consisted of 30 items but was later expanded to 36 items. The Turkish validity and reliability study of the scale was adapted into Turkish by Aksoy and his colleagues in 2019. In the Turkish adaptation study, the Cronbach's Alpha value was reported as 0.94 (15). In this research, however, the Cronbach's Alpha value was found as 0.965.

Coronavirus Anxiety Scale (CAS): In 2020, to identify potential cases of dysfunctional anxiety associated with the COVID-19 crisis, the Turkish validity and reliability study of the scale developed by Lee et al. was conducted by Biçer et al., with a reported Cronbach's alpha value of 0.832. In this research, the Cronbach's alpha value was found as 0.898. The CAS is in a five-point Likert type and consists of 5 questions and one dimension. In scoring the scale, "never" was scored as 0 points, "rarely" and "less than one or two days" answers 1 point, "a few days" answer 2 points, "more than seven days" 3 points, and "almost every day in the last two weeks" was scored as 4 points. The total score gives the coronavirus anxiety score. The minimum score is 0, and the maximum score is 20. A high score indicates that the experienced level of anxiety in coronavirus is high (16).

Evaluation of the Data

Data were analyzed using a statistical program. Numbers and percentages are presented. Histograms were used to determine conformity to the normal distribution, skewness, and kurtosis values were examined, and Kolmogorov-Smirnov analyses were performed. Mann Whitney U test and Kruskal Wallis tests were employed between certain obstetric characteristics and the total scores of PSRS and CAS. Logistic regression analysis was used to determine whether pregnant women felt safe or not during the epidemic process. Spearman correlation analysis was carried out between the PSRS and CAS and other quantitative variables. $p<0.05$ was accepted as a statistical significance level.

Ethical Aspect of the Study

Ethics committee approvals were received from the Ministry of Health Scientific Research Platform (03.06.2020) and the Clinical Research Ethics Committee of Giresun University (09.11.2020/12). Pregnant women were informed within the scope of

the Declaration of Helsinki principles. When the link was opened, explanations about the study were included on the first page of the questionnaire form. Those who consented to participate in the study were allowed to see the next questions. Approvals were obtained from the researchers who conducted the validity and reliability study of the measurement tools.

Results

The mean age of the participants in the study was 29.31±4.53 (Min-Max: 20-46, Median: 29). Some of the characteristics of pregnant women are presented in Table 1.

Table 1. Some of the Characteristics of the Participants (N = 204)

	Mean±SD	Median	Min.	Max.
Age of marriage	24.54 ± 3.78	25.00	15	37
Years of marriage	4.97 ± 4.45	4.00	0	20
Gestational age	27.58 ± 8.14	28.00	14	41
Number of pregnancies	1.77 ± 0.93	2.00	1	6
Number of miscarriages	0.24 ± 0.57	0.00	0	3
Number of abortions	0.15 ± 0.78	0.00	0	3
Number of surviving children	0.62 ± 0.78	0.00	0	3
Mean of anxiety	5.20 ± 2.97	5.00	0	10
The risk of COVID-19 transmission anxiety perception	6.03 ± 2.93	7.00	0	10

Primary education graduates account for 19.6% of the study, higher education graduates account for 28.8%, and secondary school graduates account for the remaining (28.4%). While 14.7% of participants reported low income, 74.5% stated that their income and expenses were equal. 89.7% claimed to be part of a nuclear family, 6.9% reported that their spouses did not work, and 9.8% stated they lacked health insurance.

80.4% of the pregnant women stated that their pregnancy was planned. While 44.6% of participants identified health staff as their source of information regarding pregnancy, 18.1% identified books, 15.7% identified personal experiences, 13.7% identified the online environment, and 7.8% identified their inner circle as the primary source of information. 11.3% of the participants stated cohabiting with someone in the risk group for COVID-19 (the elderly, children, health personnel). The rate of those who reported that they or one of their cohabitants had been diagnosed COVID-19 is 10.4%. Of the participants 61.8% reported that the process had a negative impact on their mental health, while 34.3% reported that the process had a negative impact on their physical health. In case of a health-related complaint, 57.4% indicated that they would visit a hospital, 21.1% would contact a health hotline, 12.7% would visit a community clinic, 3.9% would seek advice from others who had similar complaints, 3.9% would seek information online, and 1.0% stated that they would wait for the complaint to go away. 46.1% of pregnant women reported consulting coping strategies (music, exercise, hobbies, etcetera.) to deal with the process, 26.0% avoided watching the news, while 27.9% indicated that they did not require any application to cope with the process. 49.0% of pregnant women reported that the pandemic altered their sleep pattern, 45.1% their diet, 55.4% their exercise routines, and 86.3% their interpersonal interactions. 57.8% of pregnant women stated that the pandemic could have negative consequences for their pregnancy.

The mean scores of the scales used in the study are 42.99 ± 24.58 (Min-max: 6-116, median: 40) for PSRS, 2.60±3.26 (Min-max: 0-19, median: 2) for CAS.

As shown in Table 2, future anxiety in pregnant women during the pandemic period is 8.73 times more effective in terms of not finding the precautions taken sufficient, 0.91 times in terms of age, 0.37 times in terms of working, and 0.32 times in terms of having pregnancy-related issues ($p<0.05$).

A positive correlation has been observed between the PSRS scores of the pregnant women, their CAS scores, and their weeks of gestational age, as well as between their CAS scores and gestational age (Table 3).

The distribution of PSRS and CAS scores according to sociodemographic and obstetric characteristics is presented in Table 4.

Table 2. Factors affecting pregnant women's perceptions of their safety (N=204)

Variables	β	p	OR	95% GA
PSRS (Numeric)	-0.009	0.392	0.991	0.969 - 1.012
CAS score (numerical)	0.035	0.651	1.036	0.890 - 1.206
Age (Numeric)	-0.089	0.048	0.915	0.837 - 0.999
Gestational age (numeric)	-0.025	0.355	0.975	0.926 - 1.028
Having complications with pregnancy No Yes	1.135	**0.018**	1.00 0.321	0.125 - 0.824
Having had complications during the previous pregnancy No Yes	-0.195	0.697	1.00 0.323	0.308 - 2.196
Having fears related to childbirth No Yes	-0.823	0.062	1.00 0.439	0.185 - 1.042
Finding the precautions sufficient No Yes	2.167	**0.001**	1.00 8.734	3.762 - 20.280
Having trouble showing up for checkups No Yes	-0.539	0.229	1.00 0.583	0.242 - 1.405
Taking protective health measures No Yes	0.948	0.061	1.00 2.581	0.956 - 6.965
Employment status No Yes	-0.975	**0.022**	1.00 0.377	0.164 - 0.867

Table 3. The relationship between PSRS, CAS scores, and obstetric characteristics of pregnant women (N=204)

		PSRS	CAS	Age	Years of marriage	Gestational age	Number of pregnancies
PSRS	r p	-					
CAS	r p	0.593** **0.001**	-				
Age	r p	-0.083 0.237	-0.040 0.566	-			
Gestational age	r p	0.372 **0.001**	0.268** **0.001**	0.037 0.601	0.031 0.669	-	
Number of pregnancies	r p	-0.010 0.893	0.103 0.149	0.440** **0.001**	0.753** **0.001**	-0.014 0.840	-

Table 4. Distribution of PSRS and CAS scores based on sociodemographic and obstetric characteristics (N=204)

	PSRS score		CAS score	
Sociodemographic and obstetric characteristics	Median (95% CI)	Test and p-value	Median (95% CI)	Test and p-value
Current place of residence Province County Village	 33.00 (32.56-40.33)[a] 52.50 (47.54-58.75)[a,b] 18.50 (10.64-28.35)[b]	 KW= 24.578 **p=0.001**	 1.00 (1.39-2.39)[a] 4.00 (2.91-4.51)[a] -	 KW= 21.905 **p=0.001**
Profession Housewife Worker Civil Servant Self-employed Health care worker Instructor Other	 46.00 (42.19-53.15)[a,b,c] 35.00 (22.42-44.74)[a,d] 44.50 (37.58-53.25)[d,e,f] 13.00 (13.36-37.63)[b,e,g] 42.00 (39.16-59.73)[g,h] 30.00 (21.87-38.59)[d,f,h] 33.00 (22.74-44.71)	 KW= 19.734 **p=0.003**	 3.00 (2.42-3.91) 0.00 (-0.16-3.69) 1.00 (0.72-3.12) 3.00 (1.88-3.94) 2.00 (1.68-4.18) 0.00 (0.40-2.98) 0.00 (-0.11-1.38)	 U= 17.844 **p=0.007**
Gestational age Second Trimester Third Trimester	 32.00 (30.73-40.04) 46.00 (44.28-53.47)	 U= 3458.500 **p=0.001**	 1.00 (1.44-2.67) 2.00 (2.37-3.67)	 U= 4306.000 **p= 0.045**
Pregnancy complications No Yes	 35.00 (36.03-43.34) 52.50 (48.99-64.10)	 U= 1961.000 **p=0.001**	 1.00 (1.90-2.87) 4.00 (2.25-4.72)	 U= 2585.000 **p=0.032**
Having had complications during the previous pregnancy No Yes	 35.00 (36.40-43.79) 55.00 (49.14-63.85)	 U= 1783.500 **p=0.001**	 1.00 (1.89-2.89) 3.50 (2.45-4.65)	 U= 2223.500 **p=0.010**
The fears related to childbirth No Yes	 27.50 (27.54-35.56) 50.00 (48.18-57.36)	 U= 2547.000 **p=0.001**	 0.00 (1.02-2.16) 3.00 (2.79-4.10)	 U= 3189.000 **p=0.001**
Having had problems with the previous childbirth				
No	36.50 (36.78-43.73)	U= 809.000	1.00 (1.84-2.75)	U= 1033.000
Yes	70.00 (57.01-74.25)	**p=0.001**	4.00 (3.35-6.82)	**p=0.001**
Feeling secure				
No	48.00 (47.39-60.05)	U= 2968.500	3.00 (1.29-3.42)	U= 2873.000
Yes	33.00 (33.90-41.35)	**p=0.001**	1.50 (2.13-3.13)	**p=0.001**
Finding the precautions sufficient				
No	46.00 (42.65-52.18)	U= 2968.500	3.00 (2.68-4.13)	U= 3560.500
Yes	32.00 (33.21-42.61)	**p=0.001**	0.00 (1.22-2.20)	**p=0.001**
Fear of experiencing health changes				
No	27.00 (24.68-31.80)	U= 2180.000	0.00 (0.60-1.81)	U= 2510.000
Yes	48.00 (46.89-55.53)	**p=0.001**	3.00 (2.78-3.96)	**p=0.001**
Having trouble showing up for checkups				
No	33.00 (33.19-39.98)	U= 2873.000	0.00 (1.09-1.81)	U= 1916.000
Yes	62.00 (48.58-61.93)	**p=0.001**	4.00 (3.87-5.80)	**p=0.001**
Status of taking protective measures				
No	60.00 (48.25-67.69)	U= 2104.000	4.00 (3.71-6.54)	U= 1599.000
Yes	36.50 (36.02-42.65)	**p=0.001**	1.00 (1.58-2.40)	**p=0.001**
Receiving prenatal education				
No	35.00 (35.23-42.70)	U= 2670.500	1.00 (1.67-2.68)	U= 2415.000
Yes	55.00 (47.01-60.77)	**p=0.001**	4.00 (2.80-4.71)	**p=0.001**

[a-h] It indicates the groups from which the difference originated. KW; Kruskal-Wallis test, U= Mann Whitney Test

**Significant correlation at 0.01 level, Spearman correlation

Discussion

The COVID-19 pandemic is important in terms of emotional reactions pregnant women. Pregnant women in this study stated that they did not feel safe, regarded the precautions taken as insufficient, were concerned about their health deteriorating, claimed their mental health was damaged, and their sleep-nutrition-exercise habits and interpersonal interactions were negatively impacted. Pregnant women reported that they preferred to cope with the process through coping strategies (music, exercise, hobbies etc.). While one in every two pregnant women believed the pandemic would have a negative impact on their pregnancy, only four in every five pregnant women reported taking health precautions. According to another study conducted in Turkiye, 95.8% of pregnant women adhered to isolation guidelines during pregnancy follow-up (17). On the other hand, it was reported that staying at home and maintaining social distance was important in limiting the spread of COVID-19 and that unemployment, poverty, and increased interaction significantly affected pregnant women's everyday lives and increased stress (18). Usually, during pregnancy, the thought that something might go wrong, with the influence of hormones, was anxiety-inducing for pregnant women. During the pandemic process, on the other hand, pregnant women may have been affected by all aspects of the pandemic due to fear of infecting the infant, the thought of being in a risk group, the unpredictable nature of the pandemic, fear, and the impact of restrictions (curfew, inability to access health services etc.) (19, 20). Anxiety, depression, and stress are all serious issues during pregnancy (21). They are related to side effects such as preeclampsia, nausea, vomiting, preterm childbirth, low birth weight, and a low APGAR score (22). During the pandemic, different aspects of pregnancy should be focused on, and pregnant women should receive psychological support (19).

It was determined that people living in the district and housewives had high PSRS and CAS scores. Similarly, Kahyaoglu Sut & Kucukkaya (17) stated that the risk of anxiety is higher in unemployed, pregnant women. Moreover, many countries have postponed non-emergency operations due to the pandemic, outpatient and in vitro fertilization services were disrupted, pandemic services were concentrated in hospitals, pregnant women were transferred to other hospitals due to the closure of childbirth rooms, and breastfeeding counseling and postpartum care were impacted (23).

In this study, the PSRS and CAS levels were high in pregnant women in the third trimester; a positive correlation was detected between the gestational age and the stress and anxiety score. Similarly, Saadati et al. (24) reported that pregnant women in the second and third trimesters were concerned about the consequences of the disease. However, the average health anxiety scores were significantly higher in those in the third trimester. Medina-Jimenez et al. (25) determined a significant increase in stress levels in the last trimester of pregnancy compared to the first trimester. Demir & Kılıç (20) determined that as the gestational age increased, the anxiety levels also increased significantly. Taubman-Ben-Ari et al. (26) reported that as gestational age increased, anxiety related to childbirth increased. Contrary to the findings of this study, there are also studies indicating that anxiety experienced in the first trimester is higher than in the later stages of pregnancy (3, 4). This remained a limitation of the study since the scale used was applied only to pregnant women in the last trimester. It is thought that the reason why pregnant women's scores are significantly higher in their last trimester is due to the uncertainty of the pandemic, the impending childbirth, the prohibition of direct contact with family members during childbirth, the possibility of various restrictions, and the uncertainties associated with the hospital process.

Anxiety and stress levels were high in participants who experienced difficulties during pregnancy, had difficulties with previous pregnancies and deliveries, and had a fear of childbirth. Another study determined that those who had problems during their pregnancy perceived prenatal stress more (27). During pregnancy, women may experience increased stress and anxiety associated with adverse obstetric outcomes. Stress and anxiety levels may increase during infectious disease outbreaks (4). Due to the pandemic's global expansion and impact in Turkiye, pregnant women at risk experienced increased anxiety, distress, and fear as they worried about the safety of themselves and the fetus (12). Beyond sociodemographic, obstetric, and other health-related factors, the stress associated with childbirth preparation and concerns about COVID-19 infection to self and infant may have increased women's risk of experiencing moderate or severe anxiety during the pandemic (18). According to Taubman-Ben-Ari et al. (26), pregnant women experience anxiety and psychological distress due to various factors, including the health of the fetus or family members, the risk of being infected, and concern over childbirth. Akgor et al. (22) determined that the participant's primary source of concern and distress was the fear of contracting COVID 19 during childbirth.

The present study determined that those who found the measures taken inadequate experienced more stress and anxiety. Restriction, disruption of normal routines, and decreased social and physical contact led to distress and dissatisfaction during a pandemic. It is acknowledged that receiving insufficient information about the purpose of quarantine and the measures to be taken makes people feel worse as a stress factor (28).

Anxiety and stress levels were higher in those who expressed difficulty about showing up for pregnancy checkups, concern about their health changing, and lack of safety. Pregnant women may be hesitant to go to health institutions or hospitals during an epidemic,

as they perceive them to be in risky environments (24). Ifdil et al. (29) stated that pregnant women were worried about visiting health care facilities for fear of contracting COVID-19. Kahyaoglu Sut & Kucukkaya (17) reported that 68% felt uneasy about visiting the hospital/doctor for pregnancy follow-ups due to fear of COVID-19. The anxiety and depression scores of pregnant women who were uneasy and did not show up for checkups were significantly higher. Another study revealed that the participants' primary concern was COVID-19 transmission from the hospital during follow-up and childbirth (22). It has been determined that pregnant women experience fear due to the risk of infection and postpone their prenatal examinations or prefer safer centers (12). Stress increase considerably higher in women concerned about themselves and their unborn child. The literature reported that excessive stress and anxiety might have a detrimental effect on pregnancy outcomes, the infant's well-being, and stress can result in inadequate care, obstetric complications, immune suppression, adverse health effects, and developmental, behavioral and mental problems in infants. For these reasons, recognition of prenatal stress is significant for pregnant women and infants (30). Although prenatal follow-up and non-follow-up are thought to minimize the risk of infection, they may result in more significant complications during pregnancy. The arrangements to be made should take into account the maternal and fetal health benefits.

Among the participants, those who received training about pregnancy had high PSRS and CAS scores. This situation is believed to be caused by a combination of factors, including awareness of the importance of prenatal care and the risks that may occur when care is not received as well as knowing the effects of stress during pregnancy.

In the analysis conducted on the effect of being pregnant during a pandemic on future anxiety, it was found that age, experiencing difficulties during pregnancy, believing that the measures taken were sufficient, and working independently of one another were all effective in experiencing future anxiety. The increase in anxiety among those who experience difficulties during their pregnancy may be due to the uncertainties about the future and the extent to which the infant will be affected by the problem, the uncertainty regarding the epidemic, and the economic difficulties that are encountered by working pregnant women, media news reporting that the virus is more effective in older age, the effects of the pandemic still being seen despite the precautions taken on pregnant women that think the precautions are adequate, whether much stricter precautions are necessary, and whether pandemic will continue during and after childbirth. According to the studies, pregnant women's anxiety increased throughout the pandemic; they expressed concern for their unborn children, relatives, and health and showed health anxiety (31).

Conclusion

This study determined how pregnant women were impacted by the epidemic process, which could have been caused by various factors. Among these factors, being in the last trimester, having trouble showing up for checkups, experiencing complications during pregnancy, health concerns, finding the measures insufficient, feeling unsafe, pregnancy stress, and COVID-19 anxiety were significant.

The findings may be helpful in terms of identifying pregnant women at high risk of adverse effects, providing them psychological assistance, and preventing some complications associated with prenatal stress. In addition, nurses and midwives providing care services should be aware of the increased risk due to the effects of the COVID-19 pandemic. When the pandemic is mixed with the usual stress of pregnancy, pregnant women have an increased need for advice and counseling. While the pandemic impacts people of all ages on a variety of levels, it can also affect the mother's and newborn's health during pregnancy, childbirth, and the postpartum period. Adopting precautionary measures, managing childbirth successfully, maintaining high-quality prenatal, childbirth, and postpartum care are important in improving mother and infant health during the pandemic.

Authorship Contribution Statement

CE, CY: Conceptualization, methodology, investigation, writing, review, editing.

All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

The Glucose/Potassium Ratio Exhibits a Predictive Role That is Both Earlier and More Efficacious Compared to the Inflammatory Response in the Context of Isolated Thoracic Trauma

İzole Torasik Travmalarında; Glukoz/Potasyum Oranı, İnflamatuar Yanıta Kıyasla Hem Daha Erken Hem de Daha Etkili Bir Öngörücü Rol Sergiler

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ABSTRACT

Background/Aim: This study was designed to elucidate the relationship between the AIS 90 thoracic score, which is commonly used to assess the severity of trauma in trauma patients, and the relatively limited studies and data available on the Glucose Potassium Ratio (GPR). Additionally, the study aims to highlight the superiority, if any, of GPR in terms of trauma severity and prognosis, along with the Neutrophil Lymphocyte Ratio (NLR), which plays an important role in trauma severity and prognosis.
Material-Methods: Between June 2020 and June 2022, individuals aged 18 and older admitted to the emergency department with isolated thoracic trauma were included in the study. Data pertaining to these patients were retrospectively analyzed with the AIS 90 thoracic score serving as the reference point. The retrospective screening data of the patients enrolled in the study facilitated the categorization of individuals into three groups based on criteria delineating outpatient treatment, hospitalization and admission to the intensive care unit. The mean values of the GPR and the NLR across these three groups were assessed utilizing Analysis of Variance (ANOVA). Tukey tests were used for homogeneous groups and Tamhane tests were used for non-homogeneous groups to determine specific groups that caused significant differences. ANOVA homogeneity was checked by the Levene test and if homogeneity could not be achieved, the Welch test was used.
Results: The analysis of 89 patients with isolated thoracic trauma revealed no statistically significant difference in the GPR values between the three groups (Levene $p < 0.05$, ANOVA $p=0.025$). However, further exploration through Tukey multiple comparisons indicated that the observed significant difference was attributable to patients admitted to the intensive care unit. Likewise, a statistically significant difference was observed between the three groups in the analysis of NLR values. (Levene $p=0.252$, Welch $p=0.028$). Following Tukey's multiple comparisons, it was determined that the significant difference could be attributed to patients hospitalized in the intensive care unit.
Conclusion: The findings of the study support the conclusion that individuals with an AIS 90 thoracic score above 3 and who need to be admitted to intensive care show higher GPR values than other groups. The association between high GPR values and heightened lung parenchymal injury was evident. Consequently, it can be inferred that a high GPR value may serve as an indicator of lung parenchymal damage, suggesting a greater need for intensive care unit admission in such patients.

Keywords: Thoracic trauma, Glucose Potassium Ratio (GPR), İntensive care unit hospitalization, Abbreviated Injury Scale(AIS 90)

ÖZ

Giriş: Bu çalışma, travma hastalarında travmanın şiddetini değerlendirmede yaygın olarak kullanılan AIS 90 torasik skoru ile Glukoz Potasyum Oranı (GPR) arasındaki ilişkiyi aydınlatmayı amaçlayan, bu konuda sınırlı sayıda mevcut çalışma ve veri ışığında tasarlanmıştır. Ek olarak, çalışma, travma şiddeti ve prognozunda önemli rol oynayan Nötrofil Lenfosit Oranı (NLO) ile birlikte travma şiddeti ve prognoz açısından GPR'nin (varsa) üstünlüğünü vurgulamayı amaçlamaktadır.
Gereç ve Yöntemler: Haziran 2020-Haziran 2022 tarihleri arasında acil servise izole toraks travması ile başvuran 18 yaş ve üzeri bireyler çalışmaya dahil edildi. Bu hastalara ait veriler retrospektif olarak incelendi ve AIS 90 torasik skoru referans noktası olarak kullanıldı. Çalışmaya dahil edilen hastaların retrospektif tarama verileri, bireylerin ayaktan tedavi, hastaneye yatış ve yoğun bakım ünitesine yatış kriterlerine göre üç gruba ayrılmasını kolaylaştırdı. Bu üç gruptaki Glukoz Potasyum Oranı (GPR) ve Nötrofil Lenfosit Oranı (NLO) ortalama değerleri, Varyans Analizi (ANOVA) kullanılarak değerlendirildi.
Homojen gruplar için Tukey testleri, homojen olmayan gruplar için Tamhane testleri kullanılarak anlamlı farklılıklara neden olan spesifik gruplar belirlendi. ANOVA homojenliği Levene testi ile kontrol edilmiş, homojenlik sağlanamazsa Welch testi kullanılmıştır.
Bulgular: İzole toraks travması geçiren 89 hastanın analizinde, GPR değerleri açısından üç grup arasında istatistiksel olarak anlamlı bir fark saptanmadı (Levene $p < 0.05$, ANOVA $p = 0.025$). Bununla birlikte, Tukey çoklu karşılaştırmaları yoluyla yapılan daha ayrıntılı analiz, gözlenen anlamlı farkın yoğun bakım ünitesine kabul edilen hastalara atfedilebileceğini göstermiştir.
Benzer şekilde, NLO değerlerinin analizinde üç grup arasında istatistiksel olarak anlamlı bir fark gözlendi. (Levene $p=0.252$, Welch $p=0.028$). Türkiye'nin çoklu karşılaştırmalarını takiben, anlamlı farkın yoğun bakım ünitesinde yatan hastalara atfedilebileceği belirlendi.
Sonuç: Çalışmanın bulguları, AIS 90 torasik skoru 3'ün üzerinde olan ve yoğun bakım ünitesine yatış gerektiren bireylerin diğer gruplara göre yüksek GPR değerleri gösterdiği sonucunu desteklemektedir. Yüksek GPR değerleri ile artmış akciğer parankimal hasarı arasındaki ilişki belirgindi. Sonuç olarak, yüksek bir GPR değerinin akciğer parankimal hasarının bir göstergesi olabileceği sonucuna varılabilir, bu da bu tür hastalarda yoğun bakım ünitesine yatış ihtiyacının daha fazla olduğunu düşündürür.

Anahtar Kelimeler: Toraks Travması, Glukoz Potasyum Oranı (GPR), Yoğun Bakım Ünitesinde Yatış, Kısaltılmış Yaralanma Skalası (AIS 90)

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Introduction

The prevalence of thoracic traumas is particularly notable in individuals within the first four decades of life. These injuries are associated with a considerable mortality rate, which can vary widely, ranging from 1% to 36%, contingent on factors such as the severity of the trauma (1-3). Blunt thoracic traumas may give rise to a spectrum of injuries, encompassing, yet not confined to, rib fractures, pulmonary contusions, and cardiac injuries. The timely identification and precise management of such traumas assume paramount significance in the preservation of lives, particularly considering their heightened rates of mortality and morbidity (4).

The laboratory markers, with their rapidity, effectiveness and robust prognostic value, provide valuable insights. Integrating them into decision-making processes can significantly enhance thoracic trauma management. The surgeon in the Neutrophil-to-Lymphocyte Ratio (NLR) in response to post-traumatic stress and hypoxia holds significance comparable to alterations in electrolyte balance. This phenomenon is integral to both local and systemic inflammatory responses (5). Decreases in serum potassium (K) levels due to intracellular entry and concurrent elevation in glucose levels represent the most notable changes in electrolyte balance in response to stress and hypoxia (6,7). Alteration in electrolyte balance, especially the Glucose Potassium Ratio (GPR), is a prognostic marker that is activated earlier than inflammatory responses. This ratio has been found useful in the evaluation of mortality and morbidity in various medical conditions such as head traumas, cerebrovascular diseases, myocardial infarction, pulmonary embolism and abdominal traumas in the literature (8-11).

Trauma scoring systems offer a standardized method for quantifying the severity of trauma, assisting healthcare professionals in making informed decisions regarding the optimal level of care and necessary interventions for patients with thoracic trauma. Among these scoring systems, the Abbreviated Injury Scale (AIS), particularly the latest revised AIS 90 Scoring system, holds considerable significance. (12,13).

This study aimed to clarify the correlation and clinical significance between the AIS 90 thoracic score, the NLR score and the GPR score.

Methods

Ethical considerations were prioritized, and approval was secured from the local ethics committee for our study (Protocol number 05-28, dated 04.05.2023). The study involved the inclusion of patients with isolated thoracic trauma who were admitted to the emergency department.

In the retrospective screening of patient data, individuals with incomplete information, concomitant trauma other than thoracic trauma, a medical history of hypertension, diabetes, renal failure, and potential drug use known to interfere with electrolyte balance were systematically excluded from the study. The analysis focused on the data of a total of 89 patients aged 18 years and older who sought medical attention at the emergency department between June 2020 and June 2022, as illustrated in Figure 1.

The retrospective data of the patients were categorized based on the AIS 90 thoracic scoring system. Variables such as age, gender and trauma-related pathologies were considered for grading. . Trauma-related pathologies were further detailed, including simple single rib/sternal fracture, multiple rib fractures (more than three), lung contusion, hemothorax, pneumothorax, vascular injury, and multiple rib fractures exceeding three. Utilizing the AIS 90 scoring table developed by Grevitt MP et al., the elucidation of trauma-related pathologies, such as simple single rib/sternum fracture, multiple rib fractures (exceeding three), lung contusion, hemothorax, pneumothorax, vascular injury, and multiple rib fractures exceeding three, was conducted in greater detail (Table 1) (14).

The demographic information, including age and gender of the study participants was systematically analyzed. Subsequently, based on the hospitalization records, the patients were stratified into three distinct groups: 1) individuals subjected to outpatient treatment (Out-Patients), 2) those admitted to general ward facilities (Hospitalized), and 3) those requiring intensive care unit admission (Admitted to Intensive care). Gross Patient Revenue (GPR) and Net Length of Stay (NLO) metrics were computed for each respective group.

Statistical Analysis

ANOVA was employed to assess the equality of the GPR and NLR averages between the groups. In determining the specific groups contributing to the observed differences in those with significant distinctions in ANOVA, Tukey tests were utilized for homogeneous groups, while Tamhane multiple comparison tests were applied for non-homogeneous groups. The Levene test was conducted to evaluate the homogeneity assumption of ANOVA, and in cases where homogeneity was not met, the Welch test was performed for groups that did not conform to the homogeneity assumption. An independent two-sample t-test was employed to assess the equality of the GPR and NLR averages between the two groups.

If the significance levels for Levene (p-value), ANOVA (p-value), and Welch (p-value) tests are all greater than 0.05, it suggests that there is no significant difference in the variances between the groups Levene, no significant difference in means among the groups ANOVA, and no violation of the homogeneity of variance assumption Welch.

Results

The study encompassed data from 89 participants, comprising 47 males and 42 females. The average age of the patients was determined as 34.41 years. Statistical analysis revealed no noteworthy distinctions between the groups concerning age and gender.

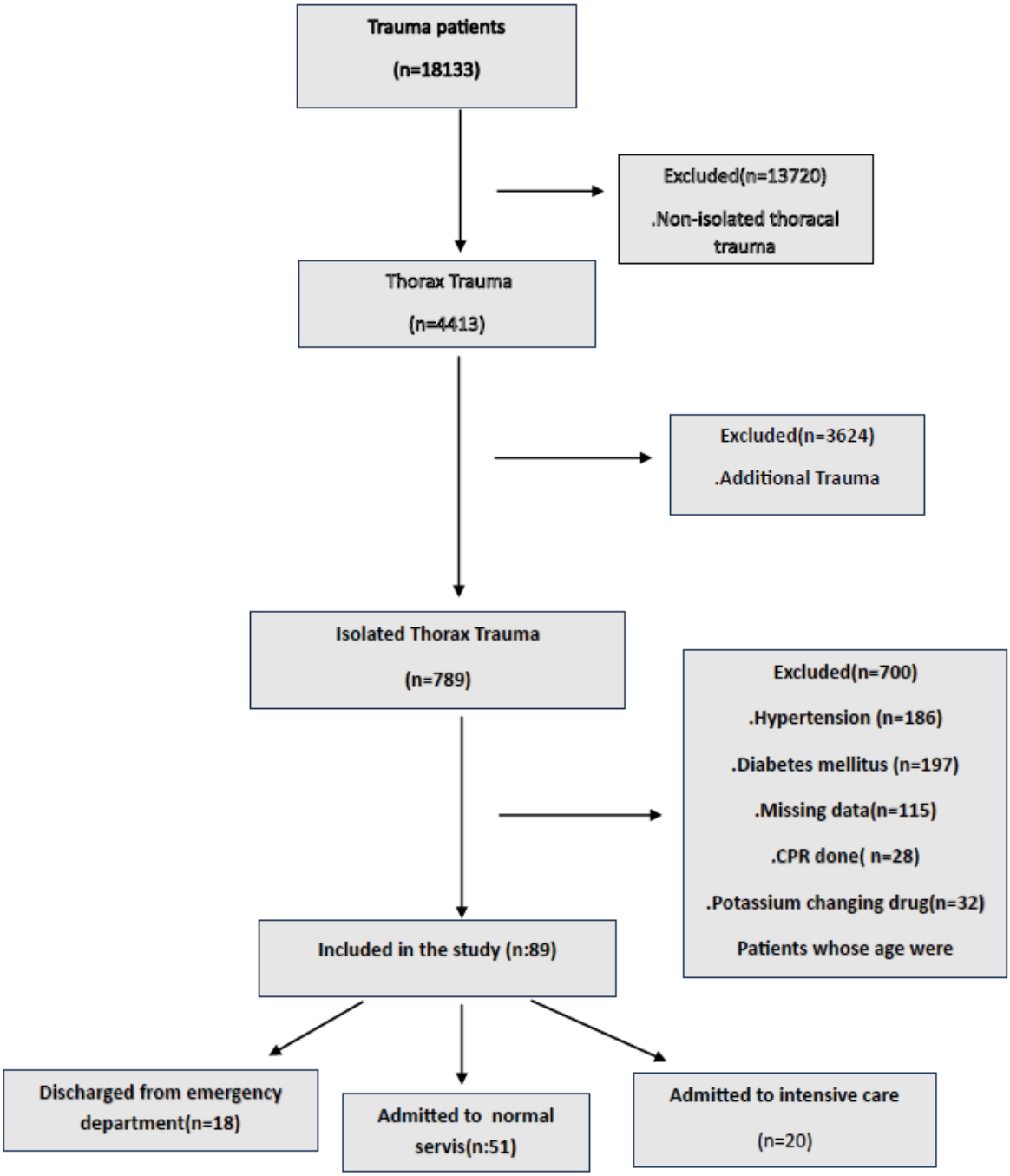

Figure1: Flowchart diagram

Out of the entire cohort of 89 patients, 18 individuals underwent follow-up in the emergency department due to trauma and were subsequently discharged. Moreover, 51 patients were admitted to the thoracic surgery service while an additional 20 patients received ongoing monitoring and care within the intensive care unit. The difference in GPR values between the groups was statistically significant (Levene p-value=0.252>0.05, ANOVA p-value=0.025<0.05) (Table 2). Tukey's multiple comparisons revealed that the difference was attributable to patients hospitalized in intensive care (Table 3). The difference between the GPR values between the groups was statistically significant (Levene p-value=0.252>0.05, ANOVA p-value=0.025<0.05) (Table 2). Similarly, the difference in NLR values between groups was statistically significant (Levene p-value=0.000<0.05, Welch p-value=0.028<0.05) (Table 2). Tukey's multiple comparisons identified that the difference was due to patients hospitalized in intensive care. The homogeneous subset obtained from pairwise comparison is detailed in Table 4. For patients with a single simple rib/sternal fracture or fewer than 3 rib fractures and an AIS 90 score <3, no significant difference was found in GPR values for the

three groups (Levene p-value=0.620>0.05, ANOVA p-value=0.566>0.05) (Table 5). Similarly, for patients with a single simple rib/sternal fracture or fewer than 3 rib fractures and an AIS 90 score <3, the difference in NLR values among the three groups is not statistically significant (Levene p-value=0.260>0.05, ANOVA p-value=0.547>0.05) (Table 5).

Similarly, the difference in NLR values between groups was statistically significant (Levene p-value=0.000<0.05, Welch p-value=0.028<0.05) (Table 2). Tukey's multiple comparisons identified that the difference was due to patients hospitalized in intensive care. The homogeneous subset obtained from pairwise comparison is shown in Table 4. For the patients with a single simple rib/sternal fracture or fewer than 3 rib fractures and an AIS 90 score <3, there was no significant difference in GPR values for the three groups (Levene p-value=0.620>0.05, ANOVA p-value=0.566>0.05) (Table 5). Similarly, for patients with a single simple rib/sternal fracture or fewer than 3 rib fractures and an AIS 90 score <3, the difference in NLR values between the three groups was not statistically significant (Levene p-value=0.260>0.05, ANOVA p-value=0.547>0.05) (Table 5).

On examining the GPR values for two groups with and without lung parenchymal damage (hemothorax, pneumothorax, lung contusion, 3 or more multiple rib fractures, vascular injury) and AIS 90 Score > 3, a statistically significant difference was observed (Levene p-value=0.000<0.05, t-test p-value=0.004<0.05). However, the difference in NLR values between these two groups was not statistically significant (Levene p-value=0.805>0.05, t-test p-value=0.597>0.05) (Table 6).

The Pearson correlation coefficient between GPR and NLR rates is 0.138 (p-value=0.198), and this correlation was statistically insignificant.

Table 1: Thoracic section of the Abbreviated Injury Scale (AIS). Uploaded by Grevitt MP, Muhivdeen HA, Griffiths C.Trauma care in a military hospital, JR Army Med. Corps. 1991. Oct;137(3):131-5. Doi:10.1136/jramc-137-03-06

AIS	Severity	Injury Description
1	Minor	Rib contusion/fracture* Sternal contusion
2	Moderate	2-3 rib fractures, stable chest* Multiple fractures of a single rib sternal fracture
3	Severe, not life-threatening	Rib fractures open/displaced/ communicated >3 rib fractures, stable chest*
4	Severe, life-threatening	Flail chest(unstable chest wall)
5	Critical, survival uncertain	Severe flail (usually requires ventilatory support
*Add AIS for the presence of haemothorax, pneumothorax,haemo-or pneu-momediastium.		

Table 2: Descriptive Statistics

		Number of Patients	Mean	Standard Deviation	Standard Error	Confidence İntervals (%95) for the mean	
						Lower Limit	Upper Limit
GPR	Hospitalized	51	32,83	15,53	2,17	28,47	37,20
	Admitted to İntensive care	20	42,35	16,09	3,6	34,82	49,88
	Out-Patients	18	30,57	9,07	2,14	26,06	35,08
	Total	89	34,51	15,09	1,6	31,34	37,69
NLR Hospitalized 51			1,78	,68	,10	1,59	1,97
	Admitted to İntensive care	20	4,75	4,74	1,06	2,53	6,97
	Out-Patients	18	1,68	,69	,16	1,34	2,03
	Total	89	2,43	2,61	,28	1,88	2,98

Tablo 3: GPR Tukey Pairwise Comparison Results

	Hospitalization Status	Number of Patients	Lower clusters for alpha= 0.05	
			1	2
Tukey HSDab	Out-patient	18	30,57	
	Hospitalized	51	32,83	32,83
	Intensive care	20		42,35
	P value		,85	,068

Tablo 4: NLR Tamhane Comparison Test Results

Hospitalization (I)	Hospitalization (J)	Mean Differences (I-J)	Standard Error	P Value	Confidence interval (%95) for the mean	
					Lower Limit	Upper Limit
Hospitalized	Intensive care	-2,97*	1,06	,03	-5,75	-,19
	Out-patient	,10	,19	,94	-,38	,58
Intensive care	Hospitalized	2,97*	1,06	,03	,19	5,75
	Out-patient	3,07*	1,07	,03	,27	5,86
Out-patient	Hospitalized	-,10	,19	,94	-,58	,38
	Intensive care	-3,07*	1,07	,03	-5,86	-,27

Table 5: Descriptive Statistics

		Number of Patients	Mean	Standard Deviation	Standard Error	Confidence İntervals (%95) for the mean	
						Lower Limit	Upper Limit
GPR	Hospitalized	51	32,83	15,53	2,17	28,47	37,20
	Admitted to İntensive care	20	42,35	16,09	3,6	34,82	49,88
	Out-Patients	18	30,57	9,07	2,14	26,06	35,08
	Total	89	34,51	15,09	1,6	31,34	37,69
NLR	Hospitalized	51	1,78	,68	,10	1,59	1,97
	Admitted to İntensive care	20	4,75	4,74	1,06	2,53	6,97
	Out-Patients	18	1,68	,69	,16	1,34	2,03
	Total	89	2,43	2,61	,28	1,88	2,98

Tablo 6: GPR and NLR Values for Two Groups with and without Lung Parenchymal Damage

Lung Parenchymal damage (hemothorax, pneumothorax, multiple rib fractures (>3)		Number of patients	Mean	Standard Deviation	Standard Error
GPR	Yes	47	38,75	17,97	2,62
	No	42	29,77	9,08	1,40
NLR	Yes	47	2,57	1,88	,27
	No	42	2,27	3,25	,50

Discussion

In accordance with the AIS 90 Thoracic scoring system, patients with thoracic trauma whose scores surpassed 3 within the initial 6 hours following emergency admission demonstrated elevated Gross Patient Revenue (GPR) compared to patients with an AIS 90 score below 3. Consequently, individuals presenting with isolated thoracic trauma and exhibiting heightened GPR values are recommended for referral to the intensive care unit to ensure comprehensive monitoring and appropriate medical intervention.

The absence of statistical significance in GPR and NLR values concerning outpatient treatment, hospitalization or intensive care unit admissions in patients with a single simple rib/sternal fracture or an AIS score of 90<3, and in those with fewer than <3 rib fractures, suggests that GPR is comparably effective as NLR in assessing trauma severity. This observation underscores the potential utility of GPR as a valuable and equivalent marker in gauging the severity of trauma.

In cases of thoracic trauma associated with lung parenchymal injury, the significance of the GPR value was noteworthy when the AIS exceeded 3, whereas the NLR did not exhibit statistical significance within the same patient cohort. This implies that considering the maximum length of stay in the emergency department is 24 hours, GPR can be regarded as an early predictive marker within the initial 24 hours post-trauma, potentially indicating a correlation with the severity of trauma experienced. The observed difference between GPR and NLR values in the context of thoracic traumas with lung parenchymal injury can be elucidated by acknowledging that NLR is inherently correlated with trauma severity and tends to function as a late predictive marker for both mortality and morbidity (15). The distinct temporal dynamics and sensitivity of these biomarkers contribute to their varied roles in reflecting trauma-related outcomes.

In conclusion, the GPR emerges as a promising biomarker for swiftly and effectively assessing the prognosis of emergency department admissions. The observed correlations between GPR values and various trauma-related outcomes, particularly in the context of thoracic traumas with lung parenchymal injury, suggest its potential utility as an early predictive marker for patient prognosis in the acute setting. Further research and validation may solidify its role in clinical practice. In the light of the dynamics observed with the NLR, which tends to enhance its effectiveness within the hospital or on the days following hospitalization, the practice of keeping patients with predictive significance in terms of mortality and morbidity for a maximum of 24 hours seems appropriate for the diagnostic window. Contrastingly, in the context of emergency departments, GPR emerges as a notably more suitable predictive marker. It helps to ensure that patients are promptly referred to the appropriate care units, facilitating timely and accurate treatment decisions, as supported by relevant references (16,17).

Based on the findings of this study in isolated thoracic traumas, there is a basis for further investigations examining the impact of GPR on prognosis within emergency departments. Subsequent studies with larger patient cohorts and exploration across diverse pathologies could provide additional insights into the utility and generalizability of GPR as a prognostic marker. Such research endeavors would contribute to a more comprehensive understanding of the role of GPR in emergency medicine and its potential implications for patient outcomes.

Acknowledging the novelty and limited extant research on GPR as a rapid and effective biomarker, it is crucial to recognize the principal limitations of our study. Notably, the study was conducted with a relatively restricted patient sample. Additionally, the exclusion of patients with known comorbidities and drug usage implemented to minimize potential influences on electrolyte balance and hyperglycemia, may impact the generalizability of the findings. Furthermore, the choice of trauma scores utilized in different studies can introduce variability and should be considered in the context of the broader research landscape. Future

studies with more extensive and diverse participant groups may help address these limitations and provide a more nuanced understanding of GPR's applicability as a biomarker.

The meticulous understanding of the profound impact of trauma, coupled with the implementation of judicious follow-up and treatment protocols, stands as a pivotal determinant in mitigating both mortality and morbidity rates within the demographic of trauma patients, as corroborated by existing literature (1,3). To assess the gravity of trauma in emergency departments, numerous trauma severity scores have been delineated in the literature, encompassing parameters such as patients' clinical profiles, vital signs, laboratory results and imaging findings. The utilization of scoring systems is designed to expedite an early assessment of trauma severity. In our investigation, we employed the AIS 90 trauma severity scoring system to assess patients who presented with isolated thoracic trauma (18,19).

Irrespective of the trauma's mechanism or the body region it impacts, trauma serves as a physiological stressor prompting various metabolic responses. One well-recognized metabolic response to stress is the initiation of an inflammatory reaction. In recent years, the literature has underscored the significance of NLR as a paramount biomarker of the inflammatory response. Notably, it has gained recognition as a predictive indicator for mortality and morbidity in various medical conditions including sepsis, infections, cerebrovascular diseases among patients in intensive care settings (20,21).

The study aimed to assess the predictive capacity of mortality and morbidity in trauma patients. However, existing research suggests that the rise in NLR values in response to stress tends to occur relatively late, typically manifesting around 5-7 days. This delayed increase in NLR underscores its significance as a late predictor in determining mortality and morbidity outcomes for patients within hospital or intensive care settings, as well as for postoperative patients (22-24).

Hence, there is a pressing need for swifter and more efficacious markers in diagnosing, appropriately monitoring and treating patients in the emergency department.

In instances of trauma-related stress exposure, the GPR exhibits an increase concomitant with heightened catecholaminergic discharge in metabolism. This is facilitated by the extrusion of intracellular glucose from cells and the reduction in serum potassium attributable to hyperglycemia, with a concurrent influx of potassium into cells through the same mechanism.

The outcomes of the study, strategically designed to anticipate that the body's reaction to stress could be as potent as, if not faster, the inflammatory response, are poised to significantly enhance hospitalization planning for individuals presenting to the emergency department with isolated thoracic trauma. It is anticipated that the findings will make a significant contribution to this issue by providing appropriate timing, meticulous follow-up and personalized treatment strategies. (25-28).

Conclusion

In conclusion, GPR values can be used as faster and more effective predictive markers compared to NLR in assessing trauma severity and determining patient prognosis in emergency department trauma management.

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Ethical considerations: This study was carried out after the approval of the local institutional review board (Konya City Hospital Ethical Committee, 04.05.2023, 05-28)

Data Sharing Statement: The entire deidentified dataset, data dictionary, and analytic code for this investigation are available upon request, from the date of article publication by contacting Demet Doctor, MD, at email dr_demetacar@hotmail.com

Author contributions: Demet Acar conceived the study and designed the trial. Demet Acar and Emine Kadıoğlu supervised the conduct of the trial and data collection. Demet Acar and Nazlı Karakuş Kenan undertook the recruitment of participating centers and patients and managed the data, including quality control. Asiye Müminat Çap provided statistical advice on study design and analyzed the data; Emine Doğan chaired the data oversight committee. Demet Acar drafted the manuscript, and all authors contributed substantially to its revision. Demet Acar and Yavuz Yılmaz take responsibility for the paper as a whole.

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ORIGINAL ARTICLE

Examination of Colposcopy Results Performed at a Single Tertiary Level Center

Üçüncü Basamak Bir Merkezde Yapılan Kolposkopi Sonuçlarının İncelenmesi

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ABSTRACT

Background: Colposcopy is the evaluation of the lower genital system (cervix, vagina and vulva) in women. Cervical cytology is the screening test for malignancy of the lower genital system, especially cervical cancers. An abnormality may be found in approximately 10% of patients undergoing cervical cytology and further investigation is required in these patients. At this stage, colposcopy is performed.
Aim: The purpose of this study was to examine the results of colposcopy performed in Konya City Hospital.
Methods: In our clinic, which is a tertiary health center, 3% acetic acid is used during colposcopy examination and Shiller test is performed if necessary. Biopsies are performed in appropriate areas. In this study, colposcopy results performed over a 2-year period were examined retrospectively. During this review, 189 patient files were scanned. Demographic data, smear, human papillomavirus (HPV) and biopsy results were collected from the patients' files and analyzed.
Results: An abnormal pathology result was observed in 177 of the biopsies performed during the 189 colposcopy examinations. (Abnormal: atypical glandular cells, acanthosis, atypical squamous cells that cannot be classified as high-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, low-grade squamous intraepithelial lesion, squamous cell carcinoma). Other colposcopic biopsy results; atrophy, erosion and squamous metaplasia. Colposcopic biopsy results were normal in only 12 patients.
Conclusion: Risk-based management is recommended for the management of malignant or premalignant cervical lesions in women with or without HPV.

Keywords: Colposcopy, Human papillomavirus, Pap Smear, Risk Based Management

ÖZ

Arkaplan: Kolposkopi kadınlarda alt genital sistemin (serviks uteri, vajina ve vulva) değerlendirilmesidir. Servikal sitoloji, alt genital sistemdeki malignitelerin, özellikle de rahim ağzı kanserlerinin tarama testidir. Servikal sitoloji yapılan hastaların yaklaşık %10'unda anormallik bulunabilir ve bu hastalarda ileri tetkik yapılması gerekir. Bu aşamada kolposkopiye başvurulur.
Amaç: Bu çalışmanın amacı, üçüncü basamak bir hastane olan Konya Şehir Hastanesi'ndeki yapılan kolposkopi sonuçlarını incelemektir.
Metod: Üçüncü basamak bir sağlık merkezi olan kliniğimizde, kolposkopi incelemesi sırasında, %3 asetik asit kullanılmaktadır ve gerekli görülürse Shiller test yapılmaktadır. Uygun görülen yerlerden biyopsi yapılmaktadır. Bu çalışmada 2 yıllık süreçte yapılan kolposkopi sonuçları retrospektif olarak incelendi. Bu inceleme ırasında 189 hasta dosyası tarandı. Hastaların dosyalarından, demografik veriler, smear, human papilloma virüsü (HPV) ve biyopsi sonuçları toplanarak analiz edildi.
Bulgular: Yapılmış olan 189 kolposkopi incelemesi sırasında yapılan biyopsilerden 177'sinde anormal bir patoloji sonucu izlendi. (Anormal: atipik glandüler hücreler, akantosiz, atipik skuamöz hücreler-yüksek dereceli skuamöz intraepitelyal lezyon olarak sıfıflandırılamayan, yüksek dereceli skuamöz intraepitelyal lezyon, düşük dereceli skuamöz intraepitelyal lezyon, skuamöz hücreli karsinom). Diğer kolposkopik biyopsi sonuçları; atrofi, erozyon ve skuamöz metaplazi. Sadece 12 hastadan yapılan kolposkopik biyopsi sonucu normal sonuçlandı.
Sonuç: HPV'li veya HPV'siz kadınlarda malign veya premalign servikal lezyonların tedavisinde risk bazlı yönetim önerilmektedir.

Anahtar Kelimeler: Kolposkopi, Human papilloma virüsü, Pap Smear, Risk Esaslı Yönetim

Introduction

Colposcopy is the evaluation of the female lower genital system (cervix, vagina and vulva) with the help of light and magnification. It was first applied by Hinselmann in 1925 (1). Although the main purpose of the colposcopy method is to use it in the evaluation of premalignant lesions of the cervix, it is also used in the presence of genital warts, lichen sclerosis and Human Papillomavirus (HPV) pathologies (2). Colposcopy is primarily a diagnostic method, but is also used as a routine screening method in some countries. Cervical cytology is the screening test for malignancy of the lower genital system, especially cervical cancers. An abnormality may be found in approximately 10% of patients undergoing cervical cytology and further investigation is required in these patients. At this stage, colposcopy is performed. After staining the cervix with acetic acid,

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the cervix is examined with colposcopy and a biopsy is taken from the areas with abnormal appearance (3, 4). Thus, the presence of cervical intraepithelial neoplasia (CIN), invasive cancer and glandular cells are determined by pathological examination of the samples taken. In addition, attention is paid to the normal anatomic location of the transformation zone (TZ) during colposcopy (5).Endocervical curettage (ECC) should be performed depending on whether the transformation zone can be seen or not. It has been recommended in some publications to routinely perform ECC in patients with HPV-16 positive tumors, even if colposcopy and cytology results are normal (6, 7). Another use of colposcopy is in the follow-up of these lesions in women with known premalignant cervical lesions.

With the colposcopy device, the cervix is enlarged 6-40 times and illuminated. Low and medium magnifications are used at first; the cervix and upper vagina are evaluated at low magnification. Magnifications of 20 times and above are used to examine vascular patterns (8). In addition, the vascular structures of the cervix are seen better with the green filter. If blood and mucus is covering the image area, it can be cleaned with a cotton swab. Even lesions that are considered to be benign (cervical polyp, wart, naboth cyst, etc.) should be noted.

Reporting the Colposcopy Result: The evaluation should be recorded immediately after the colposcopy examination is finished. The recommended colposcopy record should be as follows; 1) indication, 2) degree of cytological abnormality, 3) whether the examination is satisfactory (according to the entire squamocolumnar junction), 4) whether the lesion has a vaginal and/or endocervical continuation, 5) whether there is acetowhite epithelium (if any, it should be indicated clockwise and marked on the graph), 6) Schiller test positivity (yes/no), 7) degree of change, 8) colposcopic lesion impression, 9) recommended treatment (re-evaluation or treatment) (9).

The aim of this retrospective, cross-sectional study was to evaluate the results of colposcopy examinations performed in Konya City Hospital.

Materials and Methods

Approval for this study was obtained from the Local Ethics Committee (9.30.2022- 22/483) and all procedures complied with the provisions of the 1995 Declaration of Helsinki (Brazil as revised in 2013). This study is a retrospective cross-sectional study. No interventional procedures were performed on the patients for the study.

The number of samples calculated based on previous studies on a similar subject was determined as at least 154 (confidence interval 95% and margin of error 5%). Indications and pathology results of 189 colposcopy examinations performed at Gynecology and Obstetrics Clinic of Konya City Hospital, which is a tertiary center, were evaluated between 10 August 2020 and 26 August 2022. According to the power analysis, this number was sufficient for analysis. The patients included were females aged 25-69 years who underwent colposcopy in the defined period. The study exclusion criteria were age <25 years or > 69 years, no colposcopy examination, or cytology abnormalities that did not have an indication for colposcopy in liquid-based cytology results or results of colposcopy not performed in our hospital.

The study was planned to be retrospective and cross-sectional, and no extra invasive procedures were applied to the patients. The files of the patients who underwent colposcopy between the specified dates were scanned. Demographic data such as age, height, weight, and body mass index (BMI) of the patients were obtained from the patients' records. Liquid-based cytology results (HPV positivity and cytology) obtained before colposcopy were recorded. It was recorded whether or not the transformation zone was seen during colposcopy. After colposcopy, the pathology results of cervical biopsies taken with colposcopy and ECC, if performed, were learned from the file records. Based on these pathology results, whether further treatment was applied, if so, which treatment was applied, and whether material was sent to the pathology laboratory during this treatment, the results were scanned from the files and recorded.

Performing the colposcopy: A cotton swab impregnated with 3% and 5% acetic acid is placed on the cervix and expected to contact the cervix for 10 seconds, then the cervix is examined with colposcopy. The lesions seen are described and recorded clockwise. If the patient permits and conditions are suitable, the lesions are photographed. The Schiller test is applied using Lugol's solution with a content of 1% iodine, 2% potassium iodide and 97% distilled water to better identify the atypical epithelium with little or no glycogen. A positive Schiller test indicates that there are areas that do not retain iodine. In our clinic, 3% acetic acid is used for colposcopy. If deemed necessary during colposcopy, the Schiller test is performed and biopsies are taken from the necessary areas (10).

Statistical method: Data obtained in the study were analyzed statistically using SPSS version 28.0 software. Descriptive statistics were stated as mean, standard deviation, median, minimum and maximum values, or number (n) and percentage (%). The conformity of data to normal distribution was assessed with the Kolmogorov-Smirnov test. The Mann-Whitney U-test was used in the analysis of quantitative independent data. The Chi-square test was used in the analysis of qualitative independent data, and the Fischer test was used when the chi-square test conditions were not met. A value of $p<0.05$ was accepted as statistically significant.

Results

The clinical features of the patients, smear, colposcopy and pathology results are summarized in Table 1. The average age of patients who underwent colposcopy was 43.3. Of the 189 patients who underwent

Table 1: Smear, HPV and Colposcopy Information

		Min-Max	Median	Mean±sd/n-%
Age (years)		25.0 - 69.0	43.0	43.3 ± 9.5
Smear Result	(-) Normal			104 55.0%
	(+) Abnormal			85 45.0%
AGC				2 1.1%
ASCH				2 1.1%
ASCUS				40 21.2%
HSIL				3 1.6%
LSIL				35 18.5%
NOS				1 0.5%
Recurrent HPV				1 0.5%
Unsatisfactory				3 1.6%
HPV	(-)			36 19.0%
	(+)			153 81.0%
Colposcopy Result	(-) Normal			12 6.3%
	(+) Abnormal			177 93.7%
AGC				1 0.5%
Acanthosis				16 8.5%
ASCH				1 0.5%
Atrophic				1 0.5%
Erosion				3 1.6%
HSIL				18 9.5%
HSIL + LSIL				4 2.1%
Chronic Cervicitis				70 37.0%
LSIL				52 27.5%
SCC				3 1.6%
Squamous Metaplasia				8 4.2%

AGC; atypical glandular cells, ASCH; atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion, ASCUS; atypical squamous cells of udetermined significance, HSIL; high-grade squamous intraepithelial lesion, LSIL; low-grade squamous intraepithelial lesion, NOS; not otherwise specified, HPV; human Papillomavirus

Table 2: ECC and Surgery Information

		n	%
TZ	(-) not seen	115	60.8%
	(+) seen	74	39.2%
ECC	(-) not done	58	30.7%
	(+) done	131	69.3%
Non-existent		58	30.7%
AGC		1	0.5%
Benign		111	58.7%
LSIL		2	1.1%
Polyp		14	7.4%
SCC		2	1.1%
Squamous Metaplasia		1	0.5%
Surgery	(-)	175	92.6%
	(+)	14	7.4%
Hysterectomy		4	28.6%
Conization /LEEP		10	71.4%
CT		1	7.1%
Surgery Pathology			
Benign		5	35.7%
HSIL		4	28.6%
LSIL		2	14.3%
SCC		3	21.4%

TZ; transformation zone, ECC; endocervical curettage, AGC; atypical glandular cells, LSIL; low-grade squamous intraepithelial lesion, SCC; squamous cell carcinoma, LEEP; Loop Electrosurgical Excision Procedure, *CT; chemotherapy, HSIL; high-grade squamous intraepithelial lesion*

Table 3: Comparison of the Colposcopy Results of the HPV Groups

		HPV (-)			HPV (+)			p	
		Mean±sd/n-%		Median	Mean±sd/n-%		Median		
Age (years)		45.1 ±	10.6	45.5	42.8 ±	9.2	42.0	0.294	m
Smear Result	(-)	13	36.1%		91	59.5%		0.011	X^2
	(+)	23	63.9%		62	40.5%			
Abnormal Colposcopy Result	(-)	0	0.0%		12	7.8%		0.097	X^2
	(+)	36	100.0%		141	92.2%			
TZ	(-)	23	63.9%		92	60.1%		0.678	X^2
	(+)	13	36.1%		61	39.9%			
ECC	(-)	11	30.6%		47	30.7%		0.985	X^2
	(+)	25	69.4%		106	69.3%			
Surgery	(-)	34	94.4%		141	92.2%		0.637	X^2
	(+)	2	5.6%		12	7.8%			

[m] Mann-Whitney U-test / [X^2] Chi-square test (Fischer test)

HPV; Human Papillomavirus, TZ; transformation zone, ECC; endocervical curettage

Table 4: Comparison of the Colposcopy Groups

		Colposcopy (-)				Colposcopy (+)				p	
		Mean±sd/n-%			Median	Mean±sd/n-%			Median		
Age (years)		41.2	±	12.3	39.0	43.4	±	9.3	43.0	0.347	m
Smear Result	(-)	5		13.9%		99		64.7%		0.511	X^2
	(+)	6		16.7%		79		51.6%			
HPV	(-)	0		0.0%		36		20.2%		0.097	X^2
	(+)	11		100.0%		142		79.8%			
TZ	(-)	6		54.5%		109		61.2%		0.659	X^2
	(+)	5		45.5%		69		38.8%			
ECC	(-)	3		27.3%		55		30.9%		0.800	X^2
	(+)	8		72.7%		123		69.1%			
Surgery	(-)	11		100.0%		164		92.1%		1.000	X^2
	(+)	0		0.0%		14		7.9%			

[m] Mann-Whitney U-test / [X^2] Chi-square test (Fischer test)

HPV; Human Papillomavirus , TZ; transformation zone, ECC; endocervical curettage

HPV; *Human Papillomavirus*

colposcopy, 85 had abnormal smear results (abnormal result; any pathological consequences or unsatisfactory). HPV positivity was detected in 153 of all colposcopy results. Abnormal pathology results were detected in 177 of the colposcopy results. (Table 1).

During the colposcopy performed on 189 patients, it was found that the TZ of 115 patients could not be evaluated completely or partially. ECC was performed in 131 of 189 patients. The results were determined as benign in 111 patients, and AGC was determined in 1, L-SIL in 2, polyp in 14, squamous metaplasia in 1, and SCC in 2 patients. Surgery was applied to 14 of these patients; 10 patients underwent conization or LEEP (Loop Electrosurgical Excision Procedure), and 4 patients underwent hysterectomy (3 due to SCC and 1 patient without cervical lesion, 1 hysterectomy due to myoma uteri). One patient had received chemotherapy before surgery for SCC. Of the patients who underwent surgery, the pathology reports showed 3 SCC, 4 H-SIL, 2 L-SIL and 5 benign results. (Table 2).

The age of the patients did not differ significantly ($p>0.05$) between HPV(-) and HPV (+) groups. The rate of positive smear result in the HPV(+) group was significantly lower than in the HVP(-) group ($p<0.05$). (Table 3) (Figure 1). Abnormal colposcopy result, TZ, ECC rate, surgery rate showed no significant difference between the HPV(-) and HPV (+) groups ($p>0.05$). (Table 3).

The patients were divided into two groups as those with and without any pathology in colposcopy. The age of the patients did not differ significantly ($p>0.05$) between the groups. (Table 4). There was no significant difference between the groups in respect of abnormality in the smear result, TZ and ECC rate ($p>0.05$). (Table 4).

Discussion

Cervical cancer is one of the most frequently diagnosed gynecological malignancies in developing countries (8). HPV is an important risk factor for cervical cancer (11, 12). Risk-based management is recommended for the management of malignant or premalignant cervical lesions in women with or without HPV, and colposcopy has an important role in this management (13, 14).

The majority of smear results were reported as normal. ASCUS and LSIL were the most common abnormal smear results. 81% of all patients who underwent colposcopy were positive for any HPV type. Chronic cervicitis and LSIL were most frequently detected in colposcopy results.

In a study conducted in Brazil in which smear results were examined, the rate of abnormal findings was found as 8.9% (15). In a study by Sahin et al., atypical squamous cells of udetermined significance (ASCUS) were determined at the rate of 33.2%, atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) at 0.9%, high-grade squamous intraepithelial lesion (H-SIL) at 3.7%, and low-grade squamous intraepithelial lesion (L-SIL) at 10.7% (16). In the current study, the smear results before colposcopy were abnormal in 45% and HPV type positivity was determined in 81% of the patients. The abnormal smear results were ASCUS in 21.2%, ASC-H in 1.1%, L-SIL in 18.5%, H-SIL in 1.6%, and atypical glandular cells (AGC) were normal in 1.1% and 51%. In the same study by Sahin et al., the results of colposcopy were reported as L-SIL in 21%, H-SIL in 7%, and carcinoma in 0.5% (16). The current study colposcopy results were AGC 0.5%, ASC-H 0.5%, L-SIL 27.5%, H-SIL 9.5%, L-SIL+H-SIL 2.1%, chronic cervicitis 37%, SCC 1.6% and squamous metaplasia in 4.2%. The results were normal in 6.3%.

The transformation zone (TZ) was observed in 39.2% of the patients during colposcopy, but not in 60.8%. Endocervical curettage (ECC) was performed in 69.3% of the patients. The pathology results were reported as normal in 30.7%, 0.5% AGC, 1.1% L-SIL, 1.1% SCC, 7.4% polyps, 0.5% squamous metaplasia and 58.7% benign findings. These findings of the rates of ECC during colposcopy and the results reported as benign are

consistent with the study by Wang et al. (17). According to the colposcopy results in the current study, 1 patient received chemotherapy, and 10 patients underwent conization/LEEP (Loop Electrosurgical Excision Procedure). Hysterectomy was performed in 4 patients. All these surgeries were performed in accordance with risk-based management (13, 14, 18).

HPV positivity is a known important risk factor for cervical lesions. Additionally, it is reported that premalignant and malignant diseases are more common in women with HPV positive (11, 19, 20). HPV is held responsible not only for cervical cancers, but also for the formation of vulvar, vaginal, penile and anal cancers (21). In fact, according to the study by Peres et al., HPV also involves in the development of oral and pharynx cancers (22). In the current study, abnormal Pap smear findings were found more common in HPV-positive women ($p<0.05$). However, no significant correlation was detected between HPV positivity and abnormal colposcopy and ECC findings ($p>0.05$). This was attributed to the fact that colposcopy is performed according to abnormal smear findings, so consequently abnormal colposcopy and ECC findings are found at a high rate.

There were some limitations of this study. Although the standard cervical cancer screening test used in Konya City Hospital is performed as a co-test (Pap smear and HPV), this is not standard nationwide and some hospitals use Pap smears only for cervical cancer screening. Therefore, the results in our hospital cannot be generalized to the whole country. In addition, all the women included in this study had a prior abnormal co-test result and thus formed a selected subgroup of women at high risk for underlying premalignant lesions. Another limitation was the relatively low number of patients included, which resulted in very few patients in some combinations of test results, while others had a high proportion of high-grade lesions. However, the rates observed in groups of more than 10 women were seen consistent with rates in previous studies (23, 24).

Conclusion

Cervical cancer is one of the most common gynecological malignancies and can be screened in the community. There are many cervical premalignant and malignant lesions. Management of common premalignant lesions is important in the course of malignancy. In conclusion, risk-based management is recommended for the management of malignant or premalignant cervical lesions in women with or without HPV. Colposcopy has an important place in this management.

Conflict of interest: The authors declare no conflict of interest.

Informed consent: Approval for this study was obtained from the Local Ethics Committee (9.30.2022 - 22/483) and all procedures complied with the provisions of the 1995 Declaration of Helsinki (Brazil as revised in 2013) and the procedures were according to the ethical standards of the responsible committee on human experimentation. Written informed consent was obtained from each patient who participated in the study

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ORIGINAL ARTICLE

Determination of Potential Drug-Drug Interactions in Patients Using Quinolone Group Antibiotics

Kinolon Grubu Antibiyotik Kullanan Hastalarda Potansiyel İlaç-İlaç Etkileşimlerinin Belirlenmesi

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ABSTRACT

Aim: The aim of the study was to determine the potential drug drug interactions of patients receiving inpatient treatment in the intensive care unit and infectious diseases ward and using quinolone group antibiotics by using different interaction software programs.
Material and Methods: The prescriptions of 100 patients who received inpatient treatment in infectious diseases service and intensive care unit at Selçuk University Faculty of Medicine Hospital between January 2022 and December 2022 and who were treated with quinolone group antibiotics during treatment were analyzed retrospectively.
Results: Of the patients included in the study, 62 were male and 38 were female. The mean age of men was 65.76 ± 16.22 years, while the mean age of women was 68.63 ± 16.29 years. While Medscape® detected a total of 1776 interactions, this number was 1432 in Lexicomp® and 1693 in Drugs®.While 0.33% of the interactions detected in the Medscape® software program were contraindicated, 3.77% of the interactions were contraindicated in Lexicomp®. Kendall W coefficient 0.94, Chi-Square test 281.12, p <0.001 were found to be statistically significant. The software programs used to detect pDDIs are highly compatible with each other.
Conclusion: High agreement was found between software programs used to detect potential drug-drug interactions. Interaction classifications between software programs are different. Therefore, clinicians may benefit from different software programs.

Keywords: Drug interactions, Software, Quinolone, Antibiotics

ÖZ

Amaç: Çalışmanın amacı, yoğun bakım ünitesi ve enfeksiyon hastalıkları servisinde yatarak tedavi gören ve kinolon grubu antibiyotik kullanan hastaların potansiyel ilaç etkileşimlerinin farklı etkileşim yazılım programları kullanılarak belirlenmesidir.
Yöntem: Ocak 2022-Aralık 2022 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları Servisi ve Yoğun Bakım Ünitesi'nde yatarak tedavi gören ve tedavi sırasında kinolon grubu antibiyotiklerle tedavi edilen 100 hastanın reçeteleri retrospektif olarak incelenmiştir.
Bulgular: Çalışmaya dahil edilen hastaların 62'si erkek, 38'i kadındı. Erkeklerin yaş ortalaması 65,76 ± 16,22 iken kadınların yaş ortalaması 68,63 ± 16,29'dur. Medscape® toplam 1776 etkileşim tespit ederken, bu sayı Lexicomp®'ta 1432, Drugs®'ta ise 1693'tür. Medscape® yazılım programında tespit edilen etkileşimlerin %0,33'ü kontrendike iken, Lexicomp®'ta etkileşimlerin %3,77'si kontrendike bulunmuştur. Kendall W katsayısı 0.94, Ki-Kare testi 281.12, p<0.001 istatistiksel olarak anlamlı bulunmuştur. Potansiyel ilaç-ilaç etkileşimlerini tespit etmek için kullanılan yazılım programları birbirleriyle yüksek uyum içerisindedir.
Sonuç: Potansiyel ilaç-ilaç etkileşimlerini tespit etmek için kullanılan yazılım programları arasında yüksek uyum bulunmuştur. Yazılım programları arasındaki etkileşim sınıflandırmaları farklıdır. Bu nedenle, klinisyenler farklı yazılım programlarından faydalanabilirler.

Anahtar Kelimeler: İlaç etkileşimleri, Yazılım, Kinolon, Antibiyotik

Introduction

Drug-drug interaction is defined as the situation that occurs when drugs are used together and their pharmacological effects are altered by other drugs (1). Drug-drug interactions (DDIs) are mostly encountered at the pharmacokinetic level (2). As a result of the interactions of drugs with each other, results such as decreased efficacy in treatment and adverse drug reactions (ADRs) may occur (3). Potential drug-drug interactions (pDDIs) are among the leading preventable causes of ADRs. It is estimated that approximately 1% of hospitalized patients experience an ADRs due to DDIs (4). Quinolone group antibiotics have bactericidal effect on gram-negative and gram-positive microorganisms. They may interact with other drugs. They may inhibit the metabolic elimination of warfarin, theophylline and caffeine. Absorption of quinolones may be reduced by antacids, sucralfate, iron and zinc salts. They may interact with some Non-steroidal anti-inflammatory drugs (NSAIDs) and cause adverse effects in the central nervous system (CNS). As

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a result of these interactions, toxicity may be observed or treatment may fail. It is important for clinicians to manage interactions well (5-7).

The use of antimicrobial drugs in hospitals is progressively growing. Quinolones, in particular, are widely prescribed to treat respiratory tract infections, including tuberculosis, urinary tract infections, intra-abdominal infections, skin and skin structure infections, sexually transmitted diseases, and bone and joint infections. National use of quinolones in US intensive care units increased steadily (8-10). Quinolones are among the most commonly prescribed antibiotics in hospital. In two different researches conducted in inpatients, the rates of quinolone group antibiotic use were 14.4% and 15%, respectively (11, 12). The use of inappropriate combined antimicrobials can cause ADRs and economic burden (13, 14).

pDDIs are commonly observed as a result of polypharmacy, particularly in intensive care units (ICU) (15). Antibiotics used in intensive care units, especially macrolides and quinolones, can often cause clinically significant interactions (16).

Multiple software programs can be used to detect pDDIs. It is recommended to use different software programs at the same time to make the most accurate decision (17, 18). Software programs used for interaction detection may not reflect the clinical significance of interactions on their own. Various deficiencies in drug interaction databases make it necessary to manage the process according to the clinical significance of the interaction by making an individual assessment for each patient (19, 20).

The aim of the study was to determine the pDDIs of patients receiving inpatient treatment in the intensive care unit and infectious diseases ward and using quinolone group antibiotics by utilizing different interaction software programs.

Material and Methods

Study design

The prescriptions of 100 patients, who received inpatient treatment in infectious diseases service and intensive care unit at Selçuk University Faculty of Medicine Hospital between January 2022 and December 2022 and were treated with quinolone group antibiotics during treatment, were analyzed retrospectively. Patients' demographic information such as age and gender were recorded, and orders containing medications not covered by the software programs were excluded. Software programs Medscape®, Drugs®, and Lexicomp® were used to detect pDDIs in patients.

Statistical analysis

By analyzing each pDDIs using Kendall W values, the link between prospective pDDIs software was verified based on the outcomes of three severity degrees of interaction. Kendall W calculates a correlation coefficient that indicates agreement between multiple raters. Kendall W values range from 0-0.2, which denotes a little agreement, to 0.21-0.40, fair, 0.41-0.60, considerable, 0.61-0.80, significant, and 0.81-1.0, perfect (21). To do the statistical analysis, IBM SPSS 22.0 was used. The threshold of statistical significance was set at $p<0.05$.

Ethical Approval

This study was approved by the Selcuk University Faculty of Medicine Local Ethics Committee (Ethics committee approval number: E-70632468-050.01.04-486873. Date: 15/03/2023).

Results

Of the patients included in the study, 62 were male and 38 were female. The mean age of men was 65.76 ± 16.22 years, while the mean age of women was 68.63 ± 16.29 years. Men used an average of 15.73 ± 6.18 drugs while women used an average of 14.50 ± 4.27 drugs. Details are given in Table 1.

Table 1. Patient demographic status

	Male (n=62)	Female (n=38)
Age (mean, SD)	65.76 ± 16.22	68.63 ± 16.29
Number of medications (mean, SD)	15.73 ± 6.18	14.50 ± 4.27
Number of comorbidities (mean, SD)	1.79 ± 1.31	2.42 ± 1.50

SD: Standard deviation

Medscape® detected a total of 1776 interactions whereas this number was 1501 in Lexicomp® and 1693 in Drugs®.While 0.33% of the interactions detected in the Medscape® software program was contraindicated, 3.66% of the interactions were contraindicated by Lexicomp®. Details are given Table 2.

When pDDIs of quinolone group antibiotics were examined, the most frequently detected by the Lexicomp® software program was the Moxifloxacin / Ipratropium and Albuterol interaction (3.42%). In the

Table 2. Total potential drug-drug interactions detected in different software programs

	Medscape®					Lexicomp®						Drugs®			
	C (n) (%)	S (n) (%)	Monitor closely (n) (%)	Minor (n) (%)	Total	X (n) (%)	D (n) (%)	C (n) (%)	B (n) (%)	A (n) (%)	Total	Major (n) (%)	Moderate (n) (%)	Minor (n) (%)	Total
Total	6 %0.33	154 %8.67	1382 %77.81	234 %13.17	1776	55 %3.66	210 %13.99	953 %63.49	283 %18.85	- -	1501	286 %16.89	1141 %67.39	266 %15.71	1693

C: Contraindicated

S: Serious

Table 3. Potential drug-drug interactions most frequently detected with quinolones

Software program	Potential drug-drug interactions	Interaction classification	Number of interactions (n) (%)	Comments
Lexicomp®	Moxifloxacin / Ipratropium and Albuterol	B	49 %3.42	Increased ECG monitoring may be considered in patients at high risk for QT interval prolongation.
	Moxifloxacin / Methylprednisolone	C	40 %2.79	Monitor closely for tendon or joint pain.
	Tramadol / Moxifloxacin	C	33 %2.3	Monitor for evidence of hypo- or hyperglycemia during concomitant administration of agents with blood glucose-lowering effects and quinolone antibiotics.
	Moxifloxacin / Acetylsalicylic acid	C	20 %1.39	Aspirin may decrease the serum concentration of quinolones.
	Moxifloxacin / Dexamethasone	C	18 %1.25	Monitor closely for tendon or joint pain.
Medscape®	Albuterol / Moxifloxacin	Monitor closely	52 %4.42	May increase QTc interval
	Methylprednisolone / Moxifloxacin	Monitor closely	41 %2.30	Monitor closely for tendon or joint pain.
	Dexamethasone /Moxifloxacin	Monitor closely	18 %1.01	Monitor closely for tendon or joint pain.
	Moxifloxacin / Midazolam	Minor	18 %1.01	Moxifloxacin may increase midazolam levels
Drugs®	Albuterol / Moxifloxacin	Moderate	50 %2.95	Can cause arrhythmia
	Methylprednisolone / Moxifloxacin	Major	39 %2.3	Monitor closely for tendon or joint pain.
	Tramadol / Moxifloxacin	Major	34 %2	Can cause arrhythmia
	Acetylsalicylic acid / Moxifloxacin	Moderate	22 %1.29	The patient should be monitored for central nervous system side effects.

ECG: Electrocardiogram

QT: Time from the beginning of wave Q to the end of wave T

Medscape® software program, the most common interaction Albuterol / Moxifloxacin percentage was 4.42%, while this rate was 2.95% in the Drugs® software program. Moxifloxacin/ Methylprednisolone interaction was also among the frequently observed interactions (2.79%) by LexiComp®. The observation rate of the same major interaction by the Drugs® is 2.30%. The rate of observation of this interaction in the Medscape® was determined as 2.30%. Details are given in Table 3.

Kendall W coefficient 0.94, Chi-Square test 281.12, p <0.001 were considered statistically significant. The software programs used to detect pDDIs are highly compatible with each other. Details are given in Table 4.

Table 4. Comparison of software programs

Program	Kendall W	Chi-Square	p
Lexicomp®-Medscape® -Drugs®	0.94	281.12	<0.001

Discussion

Especially in intensive care units, ADRs can be observed frequently due to polypharmacy. Some of the ADRs occur due to pDDIs. Up to 79% of patients in intensive care units may be exposed to drug-drug interactions (22). Clinicians can prevent pDDIs by using different software programs.

In a multicenter study by Kuscu et al. quinolone group antibiotics accounted for 10% of pDDIs in inpatients. Moxifloxacin/Methylprednisolone pDDI are among the most common interactions (23). Also in our research, Moxifloxacin/Methylprednisolone interaction was among the most frequently detected pDDIs. In another study evaluating the interactions of antibiotics with other drugs in intensive care patients, the highest number of interactions was found by the Medscape® software program. (24). In our research, the highest number of interactions was by Medscape®.The reason for this is thought to be that the same interaction is shown again in different categorizations.

There are many research comparing software programs used for interaction detection to determine the most clinically appropriate software programs. In a multicenter observational study examining interactions and their consequences in intensive care patients reported that quinolone group antibiotics caused arrhythmia by interacting with other drugs and this constituted 3% of total interactions. Quinolone group antibiotics are among the drugs that most frequently cause DDIs (25). In our research, it was determined that 3.42% of the common interactions of quinolone group antibiotics could cause arrhythmia by the Lexicomp® software program. This rate was 4.42% by Medscape® and 4.95% Drugs®.

In a research conducted in patients hospitalized in the internal medicine ward, the interaction rate detected by the Lexicomp® software program per patient was determined as 2.62 (26). In our research, this rate was 15.01. The difference is thought to be due to the inclusion of patients receiving treatment in the intensive care unit in our research and therefore the high number of drugs used by the patients. In another research, Medscape® software program detected 4.33% serious interaction (27). In our research, this rate was determined as 8.67%. It is thought that the reason for the difference in the high rate found in our research is that the patients participating in our study used more drugs. Software programs used to support clinicians

should have high compatibility with each other. Liu et al. found moderate agreement (weighted kappa=0.473) between LexiComp® and Micromedex®. Additionally, the most interaction was detected by the LexiComp® software program (28). In a research comparing Drugs® and Micromedex® software programs, Drugs® was more sensitive in detecting pDDIs. It was stated that both software programs can be used to detect pDDIs (29). In this research, high compatibility (Kendall W= 0.94) was determined between three different software programs. Multiple research assessing the efficacy of DDI screening software tools have consistently established that Lexi-Interact exhibits a high level of sensitivity and specificity (30, 31). In a research conducted in a community pharmacy setting and comparing three different software programs, it was stated that Lexicomp®, Drugs®, and Medscape® programs showed weak compatibility with each other (32). This study was conducted in a free pharmacy setting and in a larger population. Therefore, it is thought to give different results from our study.

The most important limiting factor is that this study was conducted retrospectively. Since the study was conducted retrospectively, clinically significant interactions could not be detected. Prospective and multicenter studies are needed to eliminate this limitation.

High agreement was identified between the software programs used to detect pDDIs. The interaction classifications between software programs are different. Therefore, clinicians should use different software programs for pDDIs detection.

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ORIGINAL ARTICLE

Alpha Thalassemia in Istanbul: Distribution of Deletions in Alpha-globin Gene Cluster

İstanbul'da Alfa Talasemi: Alfa-globin Gen Kümesi Delesyonlarının Dağılımı

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ABSTRACT

Background/Aims: Alpha thalassemia is an autosomal recessive congenital disease resulting from a globin protein disorder encoded by genes in the alpha thalassemia gene cluster. It presents a wide range of clinical conditions, from mild anemia to hydrops fetalis. Alpha thalassemia trait is common in Middle Eastern and Mediterranean countries. It is included in the premarital screening program in Türkiye. The aim of this study was to determine the spectrum of alpha thalassemia deletions observed in Istanbul.
Methods: This cohort included 169 patients who were clinically suspected to have alpha thalassemia disease or carrier, and whose mutation was detected by the Multiplex Ligation-dependent Probe Amplification (MLPA) method.
Results: The identified variants were listed according to their frequencies and compared to previous studies conducted in different regions of Türkiye. In a total of 338 alleles, 61.8 % (209/338) mutations were detected. The most common variant was −a3.7 and -aMED ranked second.
Conclusion: This study reports alpha thalassemia mutations in Istanbul and reveals a different spectrum for some variants compared to previous studies in the region. This situation has been evaluated as evidence that the demographic structure in Istanbul has changed as a result of migration. Additionally, presenting the detected variants and mean hematological findings will guide genetic counseling in region.

Keywords: alpha-Thalassemia, gene deletion, alpha globin, Hemoglobin A

ÖZ

Amaç: Alfa talasemi, alfa globin gen kümesindeki genler tarafından kodlanan bir globin protein bozukluğu nedeni ile ortaya çıkan otozomal resesif kalıtsal bir hastalıktır. Hafif anemiden hidrops fetalise kadar geniş bir klinik tabloda görülebilir. Alfa talasemi taşıyıcılığı, Orta Doğu ve Akdeniz ülkelerinde yaygındır ve Türkiye'de evlilik öncesi tarama programına dahil edilmiştir. Bu çalışmanın amacı, İstanbul'da gözlemlenen alfa talasemi delesyon spektrumunu belirlemektir.
Gereç ve yöntemler: Bu çalışmada klinik olarak alfa talasemi hastalığı veya taşıyıcısı olduğu şüphesi olan ve mutasyonları Multiple-Ligand Prob Amplifikasyonu (MLPA) yöntemiyle tespit edilen 169 hastanın sonuçları değerlendirilmiştir.
Bulgular: Çalışma sonucunda toplam 338 alel içinde %61.8 (209/338) mutasyon tespit edilmiştir. En yaygın varyant −a3.7 iken, -aMED ikinci sırada yer almıştır.
Sonuç: Bu çalışma, İstanbul'da alfa talasemi mutasyonlarını rapor etmektedir ve bölgedeki önceki çalışmalarla karşılaştırıldığında bazı varyantlar için farklı bir spektrumu ortaya koymaktadır. Bu durum İstanbul'da demografik yapının göç sonucu değişmesinin bir kanıtı olarak değerlendirilmiştir. Ayrıca saptanan varyantlar ve ortalama hematolojik bulguların sunulması genetik danışmada yol gösterici olacaktır.

Anahtar kelimeler: alpha-Talasemi, gen delesyonu, alfa globin, Hemoglobin A

Introduction

Alpha (a) thalassemia is an inherited, autosomal recessive (AR) disorder caused by mutations in the alpha globin gene cluster (HBZ, HBA1, HBA2 and HBQ1 genes) located on chromosome 16 (1). The alpha thalassemia genes (HBA1, HBA2) occur in duplicate and the alpha chains are located approximately 3.7 kilobases apart. Although point mutations in one or both a-globin genes are known to cause thalassemia, deletions in these genes often cause the disease (2).

Alpha-thalassemia (a-thalassemia) presents in four clinical variations: silent carrier (deletion/inactivation of one a-globin gene (-a/aa or a+ carrier), thalassemia trait(deletion/inactivation of two a-globin genes either in cis (--/aa, or -a0 carrier) or in trans (-a/-a), hemoglobin H (HbH) (most commonly arising due to the deletion/ inactivation of three a-globin genes; --/-a), and hemoglobin Bart's hydrops fetalis (Hb Bart) syndrome (resulting from the removal/inactivation of all four alpha

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globin [a-globin] genes; --/--). Hb Bart syndrome is the most severe form, which results from severe anaemia induced congestive heart failure and leads to death during the neonatal period. HbH disease is the second form. It can show symptoms in the first years of life, but can only be detected by routine haematological tests in asymptomatic adults (3).

A wide range of hemoglobin levels can be observed in people with a-thalassemia, ranging from normal to severe anemia (Hb 15.5-7.5 g/dl). Additionally, these individuals have a decrease in mean corpuscular volume (MCV < 79 fl) and mean corpuscular hemoglobin (MCH < 27 pg) (4).

The World Health Organization (WHO) estimates that about 5% of the global population carries a mutate gene for a hemoglobinopathy, and over 330,000 newborns are impacted, primarily by sickle cell diseases (83%) and thalassemias (17%) every year (5). This condition is especially common in Southeast Asia, but also in the Mediterranean countries, the Middle East, Central Asia, India, Southern China, North Africa and South America (6).

Southern blotting, cloning of breakpoints, PCR amplification and direct sequencing have been used in the molecular diagnosis of alpha thalassemia. Next Generation sequencing (NGS) detects single point mutations, small deletions, and duplications, while Multiplex Ligation-dependent Probe Amplification (MLPA) detects copy number variants. Since mutations in alpha thalassemia may be population-specific, the most common mutation type in the region should be considered in the test selection and sequencing (4).

The high number of consanguineous marriages in our country increases the incidence of thalassemia, which is an AR disease. The prevalence rate reported for carriers of a thalassemia 0.25% in Türkiye and within the scope of National Health Policies, there is a comprehensive National Hemoglobinopathy Control Program for the prevention of hemoglobinopathies through prenatal diagnosis, genetic counseling and public education (7). In this study, we aimed to present the spectrum of alpha-globin gene deletions using MLPA method for patients suspected of having alpha thalassemia in Istanbul, the most populous city in Türkiye (province/country population: 18,65%) (8).

Material and Methods

This study included 169 individuals (85 females, 84 males) who were examined for alpha thalassemia at the Haseki Genetic Diagnosis Center between February 2021 and February 2023. The individuals underwent molecular testing because of their family history, premartial screening program, and clinical findings and hemoglobin characteristics. We performed mutation analysis in the alpha globin gene using the MLPA method. Written informed consent was obtained from the patients or their legal guardians. The study was approved by the Haseki Research and Training Hospital ethical committee (Protocol no:194-2023, dated November 01, 2023).

Blood samples (4 ml) were collected from the participants, and genomic DNA was extracted from EDTA-treated peripheral blood samples using a spin column method with the DNA isolation kit (PureLink® Genomic DNA Kits) according the manufacturer's instructions. DNA samples were stored at -20°C until further use. MLPA was performed using SALSA MLPA Probemix P140 HBA (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's protocol. Amplification products were analyzed by capillary electrophoresis on an ABI 3130 Genetic Analyzer (Thermo Fisher Scientific, MA, USA). Data were analyzed using GeneMapper 4.0 and Coffalyser.net software.

Results

In this study, the distribution of the results from 169 patients was evaluated using the MLPA method in the alpha thalassemia genes. In a total of 338 alleles 61.8 % (209/338) mutations were detected. The most common variant was −a3.7 and second most common was MED-- . All identified alpha globin variants are listed in Table 1. The subtypes of the −a3.7 mutation were also determined according to the product information sheet. Accordingly, the most common type was −a3.7 (D). Although this distinction is not official, it does indicate the breakpoints.

The average age of the patients was 24,6 years and 85 were female and 85 were male. The most common genotype found in patients was −a3.7 (34%), and the second most common variant was –MED1(9.1). The most common genotype in patients carrying mutations in both alleles was −a3.7/MED-- . The distribution of genotypes and mean value of haematological parameters (hemoglobin Hb, mean corpuscular volume (MCV), red cell distribution width (RDW), mean corpuscular hemoglobin (MCH)) of the patients is shown in Table 2. Screen shots of the Coffalyser.net software are shown in Figure 1.

Table 1: Mean values of haematologic findings of patients.

Genotype	n	%	Hb (13.4-17.2) (g/dl)	MCV (79-92.2)(fl)	RDW (11.4-14.6)(%)	MCH(27-31 pg) (%)
−a3.7/aa	59	34.9	12.2	73.4	16.9	21,3
−aMED/aa	38	22.4	9.9	69.1	20.5	19,5
−a20.5/aa	25	14.7	11.3	67.6	16.6	20,6
−a3.7/−aMED	21	12.4	8.6	69.4	27	21,1
−a3.7/-a3.7	15	8.8	11.5	68.3	14.8	20,9
−a4.2/aa	3	1.7	12.1	69.3	17.2	21,4
−a20.5/−a3.7	3	1.7	9.2	61.8	21.8	20,7
−aSEA /aa	2	1.1	11.9	69.4	18.3	21,8
−a4.2/−aMED	1	0.6	8.9	57.4	32.8	19,7
aaaanti-3.7/aa	1	0.6	11.8	67.5	16.9	28,1
aaaanti-4.2/aa	1	0.6	12.3	74.6	-	-

Legends: n: number of patients, **Hb**: Hemoglobin, **MCV**: Mean Corpuscular Volume, **RDW**: Red cell distribution width, **MCH**: Mean Corpuscular Hemoglobin

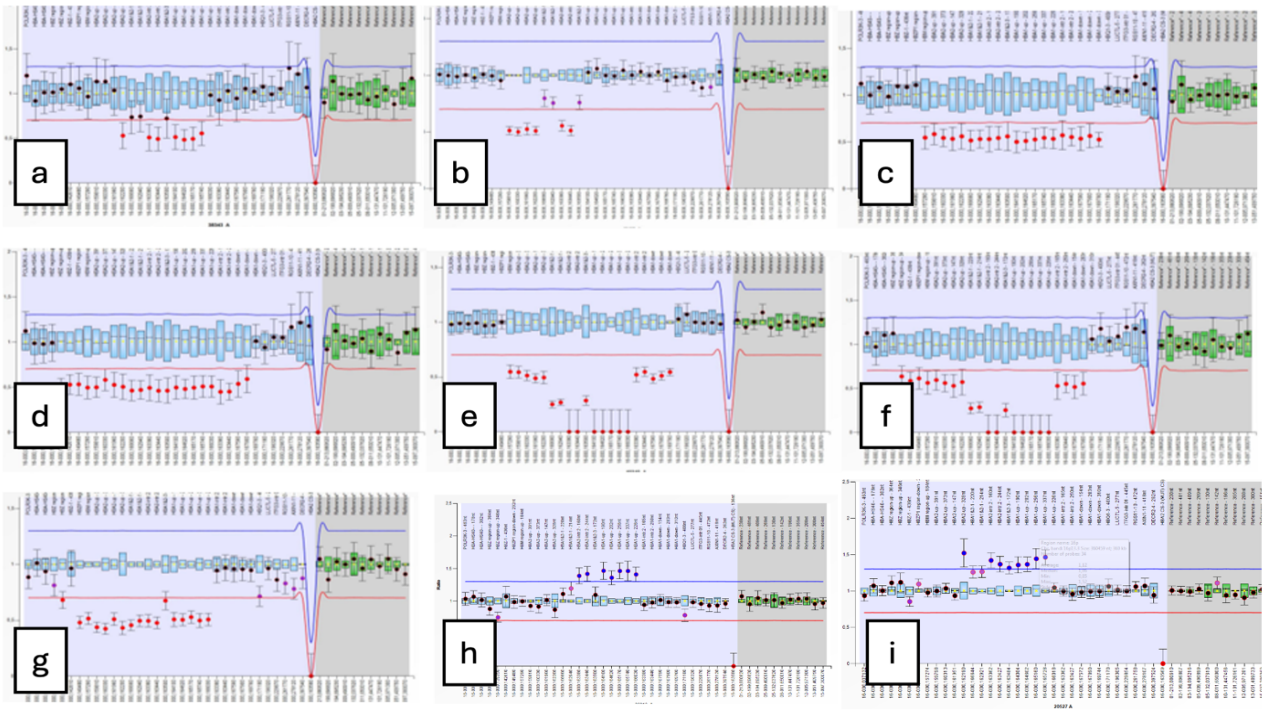

Figure 1: The images of analysis of MLPA

Legends: a: −a3.7, b: −a4.2, c: -aMED1, d: -aMED2, e: −a20.5/−a3.7 f: −a3.7/−aMED2, g: -a20.5, h: anti aaa 3.7, i: anti aaa 4.2

Table 2 Distribution of alpha globin gene deletions and allele frequencies found in previous studies in Türkiye

Variant	This study % (AC:338)	Güvenç et.al. 2010 Adana % (AC:426)	Demir et.al. 2021 Trakya % (AC:156)	Keser et.al. 2021 Antal-ya % (AC:214)	Barış et.al. 2023 West Aegean % (AC:186)
aa	37.6(127)	41 (175)	42 (65)	45(96)	41(76)
−a3.7	34(115)	43(183)	35.2(55)	42(90)	44.6(83)
−aMED	17.8(60)	10.1(43)	2.5(4)	3.7(8)	7.5(14)
−a20.5	8.2 (28)	4(17)	5.7(9)	7.5(16)	3.7(7)
−a4.2	1.2 (4)	0.7(3)	0.6(1)	-	1.1(2)
−aSEA	0.6(2)	-	1.9(3)	-	1.6(3)
aaaanti-3.7	0.3(1)	1.2(5)	9.6(15)	0.5(1)	0.5(1)
aaaanti-4.2	0.3(1)	0	-	-	-
−aHS40	-	-	0.6(1)	-	
Whole gene deletion	-	-	1.9(3)	-	
FIL/aa	-	-	-	1.4(3)	-

References :13,14,16,17, **AC**: Allele count

Discussion

Previous studies conducted in different regions of Türkiye have reported 14 different mutations, including the 3.7 kb deletion, which is the most common in alpha thalassemia (9). In studies conducted in Adana and its surroundings, where alpha thalassemia is common, the carrier rate was found as 4.1%-2.9% (10,11). In a study conducted on cord blood, the frequency of deletional alpha thalassemia carrier status was 3.6% (12). In Türkiye, the reverse dot blot method (alpha globin strip assay) has been mainly used in research studies, but recently the use of the MLPA method has increased. The comparison of the mutation frequencies we found with the frequencies from several studies conducted in Türkiye is shown in Table 2.

Due to its location, Türkiye acts as a bridge between Asia, Europe and Africa, and the province of Istanbul is the transition point of all these locations. The population of Istanbul consists of many ethnic and demographic groups due to its geographical location. The frequency of thalassemia carriage is observed high, both with migration from Anatolia and with migration from northern Iraq, Syria and other Middle Eastern countries.

In this study eight different CNV mutations were found, and one of them was triplication the others were deletions. −a3.7 deletional mutation was the most common alpha globin gene deletion (34%). In a study conducted in Istanbul in 2015, the frequency of the −a3.7 mutation was reported as 39% (13). Another study conducted in the southern region found similar diversity of mutations and reported the −a3.7 deletion frequency as 52,28% (2). The frequency of −a3.7 deletions was reported as 35,2% in a study in the Trakya region of Türkiye (14). In a study performed in the southern region of Türkiye, −a3.7 deletion frequency was reported as 44,6% and in a study performed in the Aegean Region of Türkiye was reported 43.2% (15,16). Although its frequencies differ, this mutation was the most common in all studies.

The second most common MED1/2 mutation frequency was 17.8%. In a previous study conducted in Istanbul, the rate of MED double deletion was reported as 17.9% (13). MED1/2 mutations were found with a higher frequency compared to other previous

studies (cases with point mutations are excluded) in our country (14,15,17,18). Both domestic and foreign immigrant population is concentrated in Istanbul. Although Istanbul is located in the Trakya region, detailed information on ethnic backgrounds was not available, which may be the reason for the different rates in the study conducted by Demir et al. (2021) (14).

In this study, unlike other reported studies in Turkey, an individual with the anti aaa4.2 variant (triplication) was identified, and the patient's hemoglobin level was normal. While the frequencies of other reported variants are largely similar to previous studies, regional differences are observed in their rankings (Table 1). These differences are thought to be related to regional demographic variations.

Deletions are detected in approximately 90% of alpha thalassemias (3). Therefore, presenting only deletions in this study does not cause a serious lack of data in terms of the scope of this study.

The mean hematological values provided in this study are important for genotype-phenotype correlation and will serve as a guide for genetic counseling in the region.

In regions where the carrier frequency is high, it is important to screen the population for potentially lethal diseases, especially alpha thalassemia before marriage. Nowadays, carriers of thalassemia can be determined by screening with complete blood count and hemoglobin electrophoresis before marriage in Türkiye. Molecular genetic tests are also performed depending on the results. If both spouses are thalassemia carriers, information about prenatal diagnosis and preimplantation genetic testing (PGT) should be provided, and genetic counseling should be given considering all possibilities.

Conclusion

Istanbul is the most populous city and receives a significant number of immigrants from both within and outside the country. The data we have collected is valuable as it illustrates the evolving demographic structure over the past decade. Migration due to war in Middle East countries and economic reasons from east to west have reshaped the population genetics. Consequently, while the types of mutations observed remain relatively constant due to the location of Türkiye, there has been a shift in their frequency. To track these changes more comprehensively, further studies are required.

Acknowlegements

Approvals were obtained from Haseki Training and Research Hospital Ethics Committee (Protocol no:194-2023,November 01, 2023) Study design: FNO; Data Collection: FNO; Analysis: FNO; Manuscript Preparation: FNO.

Conflict of Interest Statement

There are no conflicts of interest in this article.

Data Availability Statement

The data from the findings of the study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Nurses' Perception of Therapeutic Communication: A Metaphor Study

Hemşirelerin Terapötik İletişim Algısı: Bir Metafor Çalışması

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ABSTRACT

Background and Aim: Therapeutic communication, vital for patient centered care, is often challenging for nurses to define. Metaphors offer a valuable tool for understanding this crucial aspect. This study was conducted to explain nurses' perceptions of therapeutic communication through metaphors.
Methods: This study was conducted with metaphor analysis technique based on phenomenological approach with 189 nurses as participants. Data collection occurred via an online survey in 2023, in which participants completed the sentence, "Therapeutic communication is like ... because ...' The qualitative data were analyzed using Braun & Clarke's six-step thematic analysis method.
Results: The study identified three main themes and nine subthemes. (i)Traits: magical, complex, continuous, essential, (ii)Benefits: offering support, healing, guidance, improving (iii)Obstacles: lack of awareness.
Conclusion: Nurses perceived therapeutic communication positively, yet obstacles indicate a need for greater awareness. These findings underscore the necessity of studies to enhance nurses' skills and attitudes in therapeutic communication.

Keywords: Metaphor, nurses, therapeutic communication

ÖZ

Giriş ve Amaç: Hasta merkezli bakım için hayati önem taşıyan terapötik iletişimi tanımlamak hemşireler için çoğu zaman zordur. Metaforlar bu önemli hususu anlamak için değerli bir araç sunar. Bu çalışmanın amacı hemşirelerin terapötik iletişim algılarını metaforlar aracılığıyla tanımlamaktır.
Yöntemler: Çalışma fenomenolojik yaklaşım temelli metafor analizi tekniği kullanılarak 189 hemşirenin katılımı ile gerçekleştirilmiştir. Veri toplama, 2023 yılında katılımcıların 'Terapötik iletişim ... gibidir. Çünkü...' cümlesini tamamladığı çevrimiçi bir anket aracılığıyla gerçekleştirildi. Nitel verilerin analizinde Braun & Clarke'ın altı adımlı tematik analiz yöntemi kullanılmıştır.
Bulgular: Araştırmada üç ana tema ve dokuz alt tema belirlendi; (i)Özellikler: büyülü, karmaşık, sürekli, temel, (ii)Faydalar: destek sunma, iyileştirme, rehberlik etme, iyileştirme (iii)Engeller: farkındalık eksikliği.
Sonuç: Hemşireler terapötik iletişimi olumlu algılamaktadır ancak engeller daha fazla farkındalığa ihtiyaç duyulduğunu göstermektedir. Bu bulgular hemşirelerin terapötik iletişim konusundaki beceri ve tutumlarını geliştirmeye yönelik çalışmaların gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Hemşireler, metafor, terapötik iletişim.

Introduction

Effective communication is an integral part of patient care in all healthcare settings, from health maintenance to diagnosis, treatment and recovery of disease (1) and is essential to the execution of healthcare services (1,2). Communication is also a fundamental element of the nursing profession, enabling understanding, evaluating and attending the individual needs of each patient (3).

The importance of communication for the nursing profession has been a frequently mentioned topic by nurses and nurse scientists since Florence Nightingale (4). So much so that it has been introduced as a basic element of care from the beginning of the theory development process in nursing until today (5). For example, Peplau placed interpersonal relations, Travelbee human-to-human relations, and Orlando placed therapeutic relationship and therefore therapeutic communication at the center of nursing care with the nursing process theory.

Therapeutic communication (TC), the primary type of communication between the healthcare provider and the patient (6), is essential for the delivery of health services (1,2). Its primary purpose is to build trust to establish a meaningful relationship between the patient and nurse (6,7) and to improve patients' health, safety, and comfort (6). TC also helps build a health-focused and stress-reducing collaborative relationship between the nurse and patient (7), and improves healthcare outcomes and patients' and healthcare professionals' satisfaction (8,9). Thus, it contributes to high-quality

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(1,10,11) and patient-centered care, the universal goals of healthcare service delivery (10). In contrast, non-therapeutic communication can lead to health risks such as medicine errors and unintentional harm (12,13), as well as patient dissatisfaction (14). Considering the impact of these risks on patient care and safety, communicative competence emerges as a necessity for nursing professionals (15)

Although TC is a frequently used term in nursing and related sciences literature, it still needs to be clarified (16). Clarifying TC as a concept may contribute to strengthening nurse-patient interaction (16). It can also contribute to the development of pragmatic suggestions that will promote the advancement of nursing practices (17). Using metaphors in explaining TC can be a facilitating tool. Indeed, metaphors allow people to convey their perceptions of events (18,19) and offer the opportunity to disclose how they interpret their experiences and events (20). Metaphors make up our conceptual system and provide a means to understand how we conceptualize our experiences and make sense of that reality. Therefore, metaphorizing an expression can help individuals communicate what is hidden (21). Nurses' definition of TC through metaphors can guide future studies and evaluations on this topic. Thus, the study aims to define nurses' perceptions of TC through metaphors.

Methods

Design and sampling

This study employs a metaphor analysis based on the interpretative phenomenological approach on the qualitative design. The population of the study was nurses working in Turkey. Sample selection was not made, and data collection was terminated when the data started to repeat and saturation was reached. 244 nurses agreed to participate in the study, but 55 were excluded because they did not complete the form and thus, the study was completed with 189 nurses (n=189). The inclusion criteria were nurses working for at least one year and willing to participate in the study.

Data collection

The data were collected by an online survey application between January 2023 and June 2023. Each researcher within the scope of the study sent the form to the e-mail address of a clinician nurse and invited them to participate in the study. Nurses who agreed to participate in the study were asked to forward the form to other nurses. Thus, the form was distributed via e-mail using the snowball sampling method. The researchers and the participants did not know each other and did not meet during the research. The application allowed each nurse to fill out the form once.

Information about the demographic and working life characteristics, and experience related to therapeutic communication of the participants was collected with a structured questionnaire. Metaphor for therapeutic communication was prepared in line with the relevant literature aligning with the research purpose and includes only one question: "If you could compare therapeutic communication between patient and nurse to anything, what would it be?". The answer to this open-ended question is "Therapeutic communication is like/similar to ... Because ..." Metaphor studies often use the terms "is like/similar to" to establish a more precise relationship between the subject and the origin of the metaphor. In the first part to be filled in the form, individuals are expected to indicate their feelings, thoughts, and perceptions regarding therapeutic communication. The second part aims to determine the causes of these feelings, thoughts, and perceptions (18,20,22).

Data analysis

Quantitative data from the research were analysed using arithmetic means, minimum-maximum values, frequencies, and percentages. Arithmetic mean, minimum-maximum values, frequency, and percentage values were used in the descriptive statistics. Braun & Clarke's (23) six-step thematic analysis method was used for qualitative analysis. These steps are as follows: familiarizing yourself with your data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, producing the report.

To address transferability and confirmability; the characteristics of the sample and the study setting, as well as the characteristics of the participants, are shared (Table 1). To reinforce confirmability and credibility (24); an excerpt of the results is presented, the authors independently evaluated the data and reached consensus on themes. Since the data was collected through an online platform, participants were not interviewed face to face. Researchers and participants did not know each other. Two of the researchers (EU-GK) have a doctorate degree in psychiatric nursing, one (TP) has a master's degree in psychiatric nursing, and the other (AÖ) has a doctorate degree in nursing principles. All have worked as nurse clinicians for at least four years. The reporting of qualitative data in the study was guided by the Criteria for Reporting Qualitative Studies-COREQ guide (25).

Ethical considerations

Ethical approval of the study was obtained from the Non-Invasive Clinical Research Ethics Committee of a university (Date: 25.04.2023 / Issue No: 88). Written informed consent was obtained from the participants. The principles of the Declaration of Helsinki were complied with throughout the study.

Results

The mean age of the 189 nurses participating in the study was 34.59; their average professional working years was 11.74, and 35.2% worked in specialized units. 69.3% reported that they did not receive any training on TC (Table 1). Three themes and nine related subthemes were identified as a result of the data analysis (Table 2).

Theme 1: Traits

This theme reveals TC traits. It has four subthemes: Magical, complex, continuous and essential.

P153: "TC is like TC forest. Because it contains all kinds of colours for communication." (Magical)

P161: "TC is like a miracle. Because it makes fine touches to life." (Magical)

P112: "TC is like a video game. Because it has levels, and it progresses step by step. When you do not succeed, you are stuck at the same level until you do." (Complex)

P124: "TC is like the sky. Because sometimes it is as spacious and bright as can be, and sometimes dark and cold." (Complex)

P165: "TC is like a long narrow road. Because it continues for the rest of your career." (Continuous)

P173: "TC is like an ocean. Because it is endless, vast, and deep." (Continuous)

P46: "TC is like salt added to food. Because no matter what you add to the food, if salt is not added, the meal will not be complete; that is, the patient will not recover if there is no therapeutic communication." (Essential)

P49: "TC is like water and flower. Because the nurse is water, the patient is the flower. When therapeutic communication is not established with the patient, we cannot heal them, they dry up." (Essential)

Theme 2: Benefits

This theme focuses on the benefits of TC. It was associated with four subthemes: offering support, healing, guidance, and improving.

P14: "TC is like oxygen. Because it provides deep breathing and relaxation." (Offering support)

P28: "TC is like a blanket. Because it makes us feel comfortable." (Offering support)

P76: "TC is like a medicine. Because it cures patient's soul." (Healing)

P78: "TC is like a ship and harbour. Because every ship visits a harbour, recovers and resupplies there and moves on." (Healing)

P83: "TC is like a lighthouse. Because it provides holistic care to the patient as a 360-degree lighthouse." (Healing)

P88: "TC is like a soil and seed relationship. Because when you communicate correctly, everything can be resolved; a dry desert can become a forest." (Healing)

P103: "TC is like daylight. Because the patient blooms when they feel understood." (Healing)

P181: "TC is like a calm flowing river. Because the aim is to reach the destination, that is pouring into the sea, but carefully and confidently." (Guidance)

P184: "TC is like dolphins understanding each other underwater. Because the sound waves they emit are only meaningful to each other and guide them only." (Guidance)

P61: "TC is like going on a long trip. Because learning new things on the way means witnessing all positive and negative experiences." (Improving)

P66: "TC is like an infant. Because it grows as you put the effort in it." (Improving)

Theme 3: Obstacles

This theme demonstrates the obstacles to TC. It has only one sub-theme, lack of awareness.

P128: "TC is like burning the ships. Because you need to lift all your boundaries and talk to the patient." (Lack of awareness TC)

P131: "TC is like a mother-child relationship. Because you witness every moment of the patient's every situation, there is no privacy, and they are in need of your help." (Lack of awareness)

P148: "TC is like a favour. Because if you do not want to do it, you do not." (Lack of awareness)

Table 1. The characteristics of nurses (n=189)

Characteristic	n (%)
Gender	
Female	156 (82.5)
Male	33 (17.5)
Marital status	
Married	115 (60.8)
Single	74 (39.2)
Education level	
High school	6 (3.2)
Graduate	110 (58.2)
Post-graduate	73 (38.6)
Worked position	
Nurse	154 (81.5)
Head nurse	19 (10)
Nurse manager	16 (8.5)
Worked unit	
Internal unit	36 (19)
Surgical unit	33 (17.5)
Specialised unit*	67 (35.2)
Management unit	16 (9)
Other	37 (19.3)
Received any training on TC?	
Yes	58 (30.7)
No	131 (69.3)
	Mean (min-max)
Average age	34.59 (20-54)
Average of professional working years	11.74 (1-34)

*** Specialized unit**; Intensive care, emergency service, etc.

Table 2. The themes and subthemes of the data (n=189)

Themes	Subthemes	Metaphors
Traits	Complex (=21)	Raising a child (=1), Nested (=1), Seesaw (=1), Water (=1), Love (=1), Essence of needs (=1), Video game (=1), Touches the soul (=1), Farmer's garden (=1), Puzzle (=2), Fidelity (=1), Medicine (=1), Math question (=1), Rain (=1), Trade (=1), Flower (=1), Emotional affair (=1), Sky (=1), Game (=1), Vitamin (=1)
	Essential (=17)	Water (=4), Building block (=1), Salt (=1), Cell nucleus (=1), Mother-child relationship (=1), Water-flower relationship (=2), Key-lock relationship (=2), Key (=1), İnjection (=1), Human-conscience relationship (=1), Human-water relationship (=1), Bread-water-air (n=1)
	Continuous (=12)	Marriage (=1), Sea (=1), Mother (=1), A long narrow road (=1), Eye reflection (=1), Holy hand (=1), Medicine (=1), Marathon (=1), Fidelity (=1), Mother-father (=1), Love (=1), Ocean (=1).
	Magical (=11)	Sycamore tree (=1), Illusion (=1), Forest (=1), Living room of a house (=1), Love (=1), Google (=1), Key (=1), Magic (=1), Iceberg (=1), Magic wand (=1), Miracle (=1).
Benefits	Offering support (=43)	Mother-child relationship (=11), Mother (=6), Lone star (=1), Sibling (=2), Sea (=1), Family (=3), Confidence (=3), Oxygen (=1), Buddy (=3), Plant-soil relationship (=1), Harbour (=1), Lifeguard (=1), Vaccine (=1), Blanket (=1), Mirror (=1), Light (=1), Art (=1), Chameleon (=1), Student-teacher relationship (=1), Tree (=1), The person who is always by your side (=1)
	Healing (=37)	Prayer (=1), Mother-child relationship (=2), Key-lock relationship (=4), Savior (=1), Medicine (=11), Ship-harbour relationship (=1), Cure (=4), Lighthouse (=1), Bridge (=1), Soil-seed relationship (=1), Palliative care (=1), Phoenix (=1), Bee-pollen relationship (=1), Blackbox (=1), Hobby (=1), Sea-wave sound (=1), Cloud (=1), Song (=1), Daylight (=1), Buddy (=1).
	Guidance (=16)	Sibling (=1), Understanding (=1), Therapy (=1), Navigation (=1), Lighthouse (=2), Key-lock relationship (=2), Medicine (=1), Calm flowing river (=1), Dolphins understanding each other (=1), Bridge (=1), Mirror (=1), Understanding (=1), Candle (=1), Light (=1).
	Improving (=8)	Long trip (=1), Keystone (=1), Bridge (=1), Mirror (=1), Freedom (=1), İnfant (=1), Experience (=1), Steel rope (=1)
Obstacles	Lack of awareness (=24)	Smile (=1), Burning the ships (=1), Mother-child relationship (=13), Mirror (=2), Family (=3), Medicine (=1), Dealer-addict relationship (=1), Tree-ivy relationship (=1), Favour (=1).

Discussion

TC, an essential topic in the nursing literature (14,27) was evaluated through metaphors in this study. To our knowledge, it is the first study to demonstrate nurses' perceptions of TC through metaphors. The findings can contribute to the body of scientific evidence regarding nurses' perception of TC and guide actions to translate TC into care. The evaluations resulted in three main themes: the traits of TC, its benefits and obstacles.

The first theme analyzed in the study was the "traits" related to TC. Many traits have been attributed to TC to date, but the "magical" trait was first identified in our study. This is a remarkable finding in that it reveals how deep the nurses think the importance and impact of TC is. Nurses also defined TC as "essential" and "continuous". In the literature, TC was described as an essential element of the nursing profession to understand, assess and address each individual's needs (13). It is also emphasized that it should be applied in all healthcare processes, from health protection to the diagnosis, cure, and recovery of the disease (1). Considering that it deals with the individual's physiological, psychological, environmental and spiritual aspects (7). TC is obviously a multidimensional and complex process. This supports the "complex" aspect of TC defined by the participating nurses in our study. In a previous study, nurses commented that they believed in the power of the therapeutic relationship and used it as an essential part of their practice but had difficulty defining it (27). On the other hand, nurses in our study described positive features of TC, which is promising in enlightening the way for those needing professional support.

Another theme this study revealed was "benefits". TC is known to help nurses' better understand the problems of the individuals they care for, positively affecting and supporting them (28). TC is also cited as a crucial element in managing prognosis and treatment plans (29). Reports show that it improves care outcomes (12,13,30) and healing (14) "Not all drugs go in bottles" refers to this aspect of TC. As non-professionals, patients may lack knowledge of the illness, and nurses are at a critical position in managing this process during which they can employ the effective TC tool (16). In this way, they help the patients increase their knowledge, understanding and compliance, provide them with the opportunity to know themselves better and realize their situation, support their development, increase their health and well-being, and improve self-management (31). Given that the first step in encouraging an individual to health-promoting behaviours begins with successful communication and relationship building (32), nurses' perception that TC is beneficial may increase their likelihood of using the TC tool, thus increasing the quality of care.

Nurses' communication skills are vital in fulfilling care actions (6). Topalis says, "Communication can be as important and helpful as morphine in curing pain, or on the contrary, it can be dust or salt sprinkled on an open wound" (33). Despite being so important, nurses' "lack of awareness" about TC observed in this study represents an obstacle to TC. For example, nurses defined TC as an optional type of communication in which the patient depends on a nurse, and there are no boundaries or privacy, whereas TC is central in patient-nurse interaction (12,13,30) and it is essential for nurses to establish TC with patients to increase the quality of health services (14). Peplau (7) emphasizes that the patient and the nurse learn together in this process, and Travelbee? (34) underlines that even patient and nurse expressions should be used to facilitate communication. In addition, TC as a type of communication is based on mutual respect and commitment (16). Although the information on TC is a part of the basic nursing education curriculum in Turkiye (35), more than half of the nurses stated

that they had received no training on this subject, supporting that there may be a lack of awareness by the nurses on the subject. It is thus important to plan educational activities to increase nurses' academic equipage, competency and awareness during vocational education and to support existing nurses with in-service training programs.

Limitations

This study has some limitations. First is the metaphorical interpretation of TC, the focus of the study. Qualitative studies examining nurses' narratives in more depth are needed to provide more information. The results may involve bias depending on the nurses' professional experience, but this study may provide the basis for understanding the worldview of the nursing group. Additionally, despite the precautions taken by researchers, results may be affected by social desirability bias.

Conclusion

TC is an integral part of the nursing care process, and nurses' perceptions of TC do matter. According to the results of this study, the nurses have positive perceptions regarding the traits related to and benefits of TC. However, the TC-related obstacles pointed out a clear lack of awareness on the subject. Findings can clarify how TC is perceived as a crucial component in nursing care and suggest strategies to enhance it. They can act as a bridge between the theoretical knowledge in the literature and the nursing practice. The results can also be used in planning nursing education and research.

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ORIGINAL ARTICLE

A Comparison of Alexithymia in Individuals with Suicidal Ideation, Attempted Suicide, and Non-Suicidal Self-Injury

İntihar Düşüncesi Olan, İntihar Girişiminde Bulunan ve İntihar Amaçlı Olmayan Kendine Zarar Verme Davranışı Bulunan Bireylerde Aleksitiminin Karşılaştırılması

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ABSTRACT

Background/Aims: Alexithymia is a concept characterized by the impairment of an individual's awareness of his feelings and ability to clearly identify and describe them. This study investigated whether alexithymia levels would differ in three different groups consisting of participants exhibiting suicidal ideation, attempted suicide, and non-suicidal self-injury (NSSI).
Methods: Seventy-five patients admitted to the psychiatry clinic and emergency department due to suicidal ideation, attempted suicide, or non-suicidal self-injury and 25 healthy controls were included in the study. The Toronto Alexithymia Scale (TAS-20) and Hamilton Depression Rating Scale (HDRS) were applied to all participants. The individuals taking part were assigned into three different groups for comparisons: suicidal ideation, attempted suicide, and NSSI.
Results: TAS-20 scores and HDRS scores were higher in the patient groups than in the healthy controls ($p<0.001$). Significantly higher TAS-20 scores were determined in the group with NSSI than in the attempted suicide group. Mean scores for the TAS subscales TAS-A (difficulty identifying feelings) and TAS-B (difficulty describing feelings) were significantly higher in the NSSI group than in the attempted suicide group. Positive correlation was found between severity of depression and alexithymia levels, TAS-20 scores, TAS-A scores, TAS-B scores, and TAS-C (externally oriented thinking) scores.
Conclusion: The data from this study indicate that alexithymia levels in NSSI are higher than in individuals with attempted suicide and suicidal ideation. This finding reveals the importance of examining individuals with NSSI in terms of alexithymia as well.

Keywords: Alexithymia, attempted suicide, non-suicidal self-injury, suicidal ideation.

ÖZ

Amaç: Aleksitimi, bireyin duygularının farkına varmasında, bunları tanıma ve açıkça tanımlama becerisinde bozulma ile karakterize bir kavramdır. Bu çalışma, intihar düşüncesi olan, intihar girişiminde bulunan ve intihar amaçlı olmayan kendine zarar verme (NSSI) davranışı sergileyen katılımcılardan oluşan üç farklı grupta aleksitimi düzeylerinin farklı olup olmayacağını araştırdı.
Gereç ve Yöntemler: Çalışmaya intihar düşüncesi olan, intihar girişiminde bulunan veya intihar amaçlı olmayan kendine zarar verme nedeniyle psikiyatri kliniğine ve acil servise başvuran 75 olgu ve 25 sağlıklı kontrol dahil edildi. Tüm katılımcılara Toronto Aleksitimi Ölçeği (TAÖ-20) ve Hamilton Depresyon Derecelendirme Ölçeği (HAM-D) uygulandı. Olgular intihar düşüncesi olan, intihar girişiminde bulunan ve NSSI olmak üzere üç farklı gruba ayrılarak kendi aralarında ve sağlıklı kontroller ile karşılaştırıldı.
Bulgular: Olgu gruplarında TAÖ-20 skorları ve HAM-D skorları sağlıklı kontrollere göre daha yüksekti ($p<0,001$). NSSI grubunda intihar girişimi grubuna göre TAÖ-20 puanlarının anlamlı derecede yüksek olduğu belirlendi. TAÖ-20 alt ölçekleri TAÖ-A (duyguları tanımada zorluk) ve TAÖ-B (duyguları tanımlamada zorluk) ortalama puanları, NSSI grubunda intihar girişiminde bulunan gruba göre anlamlı derecede yüksekti. Depresyonun şiddeti ile aleksitimi düzeyleri, TAÖ-20 puanları, TAÖ-A puanları, TAÖ-B puanları ve TAÖ-C (dışa dönük düşünme) puanları arasında pozitif korelasyon tespit edilmiştir.
Sonuç: Bu çalışmadan elde edilen veriler NSSI'de aleksitimi düzeylerinin intihar girişiminde bulunan ve intihar düşüncesi olan bireylere göre daha yüksek olduğunu göstermektedir. Bu bulgu NSSI'li bireylerin aleksitimi açısından da incelenmesinin önemini ortaya koymaktadır.

Anahtar Kelimeler: Aleksitimi, intihar girişimi, intihar amaçlı olmayan kendine zarar verme, intihar düşüncesi.

Introduction

Despite having been described a long time previously, alexithymia is still a foreign concept for many clinicians. In terms of etymology, alexithymia means 'lacking words to express feelings' and is a condition characterized by the impairment of an individual's awareness of his feelings and inability to clearly identify and describe them (1). Problems encountered in an individual's awareness and expression of his feelings and selecting correct behaviors in the light of his emotions can lead to deterioration of mental well-being and a disposition to mental disorders (2). Various studies have estimated alexithymia prevalence in the community at 10–19% (3). Since more than one variable is involved in the etiology, alexithymia is defined using a multifactorial model. These include exposure to stressful events, the quality of attachment relationships in childhood, and congenital factors (4). Alexithymia is not recognized as a disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (5). Therefore, it is routinely evaluated using self-report

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scales rather than diagnostic criteria. Five principal characteristics of alexithymia are described: difficulty identifying one's own feelings, difficulty expressing one's own feelings, inability to experience emotions, an externally focused thinking style concentrating on the concrete details of events, and weak fantasizing or symbolic thinking (6). The ability to correctly interpret emotional facial expressions is of primary importance for healthy interpersonal interaction. Studies have observed deficiencies in perceiving emotions from the facial expressions of others in cases of alexithymia (7). Impaired perception of facial emotional signals can result in dysfunctional interpersonal relationships, frequently observed in alexithymic individuals (8).

Since alexithymic individuals are unable to verbally convey the problems they encounter and their feelings, they turn to physical reactions for external expression and employ a primitive method of expression in which emotions are externalized through the body (6). Patients presenting which physical symptoms of undeterminable cause represent difficult cases for primary physicians. Many such patients have lengthy histories regarding somatic symptoms similar or different to their current symptoms and usually respond weakly or are resistant to standard medical treatment. Physicians generally respond with helplessness and feelings of frustration and anger, thus making treatment even more problematic. These patients are frequently included under categories such as somatoform disorders, depressive disorders, anxiety disorders, and sometimes malingering (9).

Despite being formerly associated with psychosomatic disorders, several studies have revealed an association with depression, alcohol and substance disorder, eating disorders, autism spectrum disorders, particularly Asperger's syndrome, post-traumatic stress disorder, and personality disorders (6). Longitudinal studies have reported that alexithymia can exhibit a stable course and also represent a transient phenomenon, and that the causal relationship between it and depression is still unclear. In other words, in addition to being a chronic condition accompanying personality disorder, alexithymia can also encapsulate a transient phenomenon such as post-traumatic stress disorder. It should, therefore, be regarded as both a trait and a state phenomenon (10).

Alexithymic individuals have been observed to produce superficial and concrete solutions to problems they encounter, rather than examining the root of the difficulty. These physical forms of expression can sometimes also emerge in the form of suicide, because individuals with difficulty in recognizing their feelings are reported to be capable of regarding suicide as a solution and to externalize unspoken conflicts by means of attempted suicide (11). Although a powerful relationship has been revealed between alexithymia and psychiatric disorders, the association with suicide only began being addressed more recently (12). In addition to suicide, non-suicidal self-injury is another form of behavior widely seen in society (13). Although non-suicidal self-injury (NSSI) has a protective function against suicide in the short term, it is also a risk factor for attempted suicide since the individual develops the capacity to self-injury during this process (14). There has been reference to it serving the individual's emotional regulation or avoidance function in theoretical models of NSSI (15). The most frequently reported function of NSSI is emotion regulation, followed by self-punishment and interpersonal relationship difficulties (16). Findings supporting the idea that alexithymia is a risk factor for NSSI in the general and psychiatric populations have been published in recent years (17).

The question of the relationship between alexithymia and suicidal ideation and behavior has received little attention to date. Understanding whether or not alexithymia is a potential indicator of the risk of suicide will be an important step in selecting an appropriate method of treatment. Research in the literature has generally evaluated the relationships between alexithymia and suicidal ideation, attempted suicide, and NSSI separately. The purpose of this study was to investigate whether alexithymia levels would differ in three different groups consisting of participants exhibiting suicidal ideation, attempted suicide, and NSSI, and thus to clarify the relationship between these states.

Material and Methods

This study was performed at the Erzurum City Hospital Psychiatry Clinic and Emergency Medicine Clinic, Türkiye, with the approval of the University of Health Sciences Erzurum Medical Faculty ethical committee (Erzurum Medical Faculty no. 2023/01-02 dated 31/05/2023). The research was conducted in conformity with the principles of the Declaration of Helsinki, and informed consent was obtained from all patients and controlled prior to enrolment.

Participants

One hundred four cases admitted to the Erzurum City Hospital emergency medicine and mental health and diseases clinics due to suicidal ideation, attempted suicide, or NSSI were included in the study. Individuals with psychotic disorder, depression with psychotic features, bipolar disorder, alcohol and substance users, dissociative disorder, mental disability, epilepsy, or other neurological diseases were excluded. Eight cases were excluded due to psychotic symptoms, five due to histories of bipolar disorder, four due to neurological disease, and 12 for refusing to take part. The study was thus conducted with 100 cases (47 female and 53 male).

The controls consisted of 25 individuals presenting to the Health Sciences University Erzurum Medical Faculty Psychiatry Clinic for good health status reports and evaluated as healthy. The healthy controls enrolled in the study were matched with the patient group in terms of age and sex.

Tools

Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5/CV): This was used to

investigate Axis 1 psychiatric disorders on the basis of DSM-5. This semi-structured interview guideline was developed by First et al. for identifying principal DSM-5 diagnoses (18). The validity and reliability of the Turkish version were investigated by Elbir et al. (19).

Sociodemographic data form: The sociodemographic data form was prepared by the authors in accordance with the literature to examine the sociodemographic and clinical data of the participants.

Toronto Alexithymia Scale (TAS-20): This five-point Likert-type, self-evaluation scale, developed to investigate alexithymia, consists of 20 items and three subscales. The TAS-20 was developed by Bagby et al. (20). These subscales; difficulty identifying feelings (TAS-A), difficulty describing feelings (TAS-B), and externally oriented thinking (TAS-C). The scores that can be obtained from the scale varies between 20-100. Higher scores indicate higher levels of alexithymia. The Turkish validity and reliability study of the scale was conducted by Sayar et al. in 2001 (21). According to the Turkish version, the score to be obtained from the scale is less than or equal to 51. It has been suggested that it can be categorized as "non-alexithymic", between 52 and 58 as "borderline condition", and being equal to or greater than 59 as "alexithymic". In the internal reliability evaluation of the Turkish version, the Cronbach alpha coefficient was found as 0.78 (22).

Hamilton Depression Rating Scale (HDRS): HDRS was developed by Williams in 1978 and is the most widely used assessment scale for depression, consisting of 17 items (23). The total scale score is calculated by adding the scores for each item. Scores lower than 7 are regarded as indicating no depression, scores of 7-17 as mild depression, scores of 18-24 as moderate depression, and scores above 25 as severe depression. The Turkish validity and reliability study was conducted by Akdemir et al. (24).

Statistical Analysis

The data were analyzed on SPSS version 25.0 software. Normality of distribution of variables was examined using histogram graphs and the Kolmogorov-Smirnov test. Descriptive analyses were expressed using mean, standard deviation, and minimum-maximum values. Non-normally distributed (non-parametric) variables were compared between the groups using the Mann Whitney U test. Spearman's correlation test was applied in the analysis of measurement data. P values less than 0.05 were regarded as statistically significant.

Results

Seventy-five cases (36 female and 39 male) and 25 healthy controls (11 female and 14 male) participated in this study (Table 1). The patient and control group sociodemographic and clinical characteristics are shown in Table 1.

The alexithymia level in the healthy controls in this study was 16.00% (Table 1). The cases included in the study were divided into three subgroups; individuals with suicidal ideation, attempted suicide, and NSSI. The healthy controls' mean TAS-20, TAS-A, and TAS-B scores were lower than those in the other groups (Table 2).

Mean HDRS, TAS-20, TAS-A, TAS-B, and TAS-C scores were compared between the suicidal ideation, attempted suicide, and NSSI groups. Accordingly, the group with the highest HDRS score was the group with suicidal ideation, followed by the NSSI group, and it was lowest in the group with suicide attempts. TAS-20 score was highest in the NSSI group, followed by the group with suicidal ideation, and was lowest in the group with suicide attempts. (Table 3).

Correlations between scales were examined in patient groups. This revealed positive correlation between HDRS scores and TAS-20, TAS-A, and TAS-B scores. Analysis in the attempted suicide group revealed positive correlations between HDRS scores and TAS-20, TAS-A, and TAS-B scores. In NSSI group, positive correlations were determined between HDRS scores and TAS-20, TAS-A, TAS-B, and TAS-C scores (Table 4).

The relationship between severity of depression, and the presence of alexithymia, and TAS-20, TAS-A, TAS-B, and TAS-C scores was examined in all the case groups. Positive correlations were observed between severity of depression and the presence of alexithymia, and TAS-20, TAS-A, and TAS-B scores in all the case groups (Table 5).

Table 1: Comparison of sociodemographic and clinical characteristics of the groups

		n mean±SD	%
Total number of patients		75	
Sex	Male	39	52.00 %
	Female	36	48.00 %
Age, years		29.79±8.562	
Subgroups	Suicidal ideation	25	33.33 %
	Attempted suicide	25	33.33 %
	NSSI	25	33.33 %
Scale scores		18	
	HDRS	29.00±4.640	
	TAS-20	39	
		23.77±8.845	
Depression severity	None	3	4.00 %
	Mild	15	20.00 %
	Moderate	39	52.00 %
	Severe	18	24.00 %
Alexithymia (according to TAS)			
	None	20	26.66 %
	Probable	22	29.33 %
	Present	33	44.00 %
Control group			
Sex	Male	14	56.00 %
	Female	11	44.00 %
Age, years		25	
Alexithymia		30.40±9.428	
	None	21	84.00 %
	Probable	0	
	Present	4	16.00%

Table 2: A comparison of the case groups' TAS-20, TAS-A, TAS-B, and TAS-C scores with those of the healthy controls

	Suicidal ideation (1)		Attempted suicide (2)		NSSI (3)		Healthy controls (4)		p (1-4)	p (2-4)	p (3-4)
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	Medyan (min-max)			
TAS-20 score	56.92±13.4	60 (26-76)	50.12±13.45	53 (26-73)	60.6±10.97	61 (28-81)	38.44±11.72	39 (20-59)	<0.001	0.001	<0.001
TAS- A score	18.46±7.95	17.5 (6-36)	13.16±5.89	13 (4-26)	16.64±4.95	16 (4-27)	8.56±4.53	8 (2-19)	<0.001	0.004	<0.001
TAS- B score	16.04±8.12	15 (2-32)	18.52±6.8	20 (7-39)	23.96±6.6	23 (8-36)	9.32±3.88	9 (4-19)	0.001	<0.001	<0.001
TAS- C score	21.44±5.66	19 (14-29)	18.88±4.87	20 (10-28)	19.76±4.21	20 (10-27)	20.52±5.25	20 (11-30)	0.712	0.325	0.527

Mann Whitney-U Test, TAS: Toronto alexithymia scale, TAS-A: Difficulty identifying feelings, TAS-B: Difficulty describing feelings, TAS-C: Externally oriented thinking, NSSI: Non-suicidal self-injury

Table 3: A comparison of the case groups' HDRS, TAS-20, TAS-A, TAS-B, and TAS-C scores

	Suicidal ideation (1)		Attempted suicide (2)		NSSI (3)		p (1-2)	p (1-3)	p (2-3)
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)			
HDRS score	24.24±8.2	21 (12-41)	18.56±9.28	16 (4-42)	22.88±9.27	23 (4-39)	0.015	0.600	0.072
TAS-20 score	56.92±13.4	60 (26-76)	50.12±13.45	53 (26-73)	60.6±10.97	61 (28-81)	0.082	0.437	0.008
TAS-A score	18.46±7.95	17.5 (6-36)	13.16±5.89	13 (4-26)	16.64±4.95	16 (4-27)	0.016	0.477	0.022
TAS-B score	16.04±8.12	15 (2-32)	18.52±6.8	20 (7-39)	23.96±6.6	23 (8-36)	0.296	0.002	0.004
TAS-C score	21.44±5.66	19 (14-29)	18.88±4.87	20 (10-28)	19.76±4.21	20 (10-27)	0.213	0.572	0.585

Mann Whitney-U Test, TAS-20: Toronto alexithymia scale, TAS-A: Difficulty identifying feelings, TAS-B: Difficulty describing feelings, TAS-C: Externally oriented thinking, NSSI: Non-suicidal self-injury

Table 4: Correlations between scales were examined in patient groups

		HDRS score	TAS-20 score	TAS-A score	TAS-B score
	Suicidal ideation				
Suicidal ideation TAS-20 score	r	0.690			
	p	<0.001			
TAS-A score	r	0.650	0.858		
	p	**0.001**	**<0.001**		
TAS-B score	r	0.531	0.912	0.786	
	p	**0.008**	**<0.001**	**<0.001**	
TAS-C score	r	-0.115	-0.365	-0.478	-0.361
	p	0.585	0.073	**0.018**	0.083
	Attempted suicide				
Attempted suicide TAS-20 score	r	0,686			
	p	**<0,001**			
TAS-A score	r	0.780	0.856		
	p	**<0.001**	**<0.001**		
TAS-B score	r	0.664	0.910	0.853	
	p	**<0.001**	**<0.001**	**<0.001**	
TAS-C score	r	0.246	0.544	0.162	0.257
	p	0.236	**0.005**	0.440	0.215
	NSSI				
NSSI TAS-20 score	r	0.664			
	p	**<0.001**			
TAS-A score	r	0.410	0.691		
	p	**0.042**	<0.001		
TAS-B score	r	0.520	0.821	0.628	
	p	**0.008**	**<0.001**	**0.001**	
TAS-C score	r	0.518	0.354	-0.240	0.138
	p	**0.008**	0.083	0.248	0.509

Spearman Correlation Test, TAS-20: Toronto alexithymia scale, TAS-A: Difficulty identifying feelings, TAS-B: Difficulty describing feelings, TAS-C: Externally oriented thinking, HDRS: Hamilton depression rating scale, NSSI: Non-suicidal self-injury

Table 5: The relationship between severity of depression, and the presence of alexithymia, and TAS-20, TAS-A, TAS-B, and TAS-C scores in the case groups

	Severity of depression	
	p	r
Suicidal ideation		
Alexithymia level	0.628	**0.001**
TAS-20 score	0.691	**<0.001**
TAS-A score	0.596	**0.002**
TAS-B score	0.595	**0.002**
TAS-C score	-0.231	0.267
Attempted suicide		
Alexithymia level	0.755	<0.001
TAS-20 score	0.775	**<0.001**
TAS-A score	0.794	**<0.001**
TAS-B score	0.725	**<0.001**
TAS-C score	0.358	0.079
NSSI		
Alexithymia level	0.608	0.001
TAS-20 score	0.750	<0.001
TAS-A score	0.416	0.039
TAS-B score	0.569	0.003
TAS-C score	0.484	0.014

Spearman Corellation Test, TAS-20: Toronto alexithymia scale, TAS-A: Difficulty identifying feelings, TAS-B: Difficulty describing feelings, TAS-C: Externally oriented thinking, NSSI: Non-suicidal self-injury

Discussion

In this study, we aimed to compare alexithymia levels in three different groups consisting of participants with suicidal ideation, suicide attempt, and non-suicidal self-injury (NSSI) behavior. Previous studies have reported prevalences of alexithymia of 5-10% in women and 9-17% in men (25). A previous study involving university students determined no gender

difference in terms of alexithymic symptoms, while similar prior research reported alexithymic symptoms in 9.5% of men and 7.2% of women (26). The alexithymia level in the healthy controls in this study was 16.00%, with the values of 12.00% in women and 4.00% in men. The difference between the data from the present study and the previous literature may be due to our relatively low number of healthy controls. The alexithymia rate in the patient group in the present study was 44.00%. Previous studies involving patient groups have reported symptoms in 32.7% of outpatient psychiatric patients and 47.3% of hospitalized patients (27). Our finding is, therefore, consistent with the previous literature.

Depression severity was evaluated in the alexithymic cases in this study with mild depression being detected in 33.3%, middle depression in 48.48%, and severe depression in 18.52%. These data are consistent with the previous literature. Earlier studies have revealed a significant association between alexithymia and depression (28). Research involving depressive patients has detected significantly greater difficulty in identifying feelings, describing feelings, and total alexithymia scores in such individuals compared to a healthy group, with alexithymic symptoms being observed in approximately one third of patients with depression (29). In the present study, alexithymia was determined in 6.66% of the patients with mild depression, 41.02% of those with moderate depression, and 88.88% of those with severe depression. Severity of depression also exhibited positive correlation with alexithymia levels and TAS-20 scores ($p=0.001$ and $p<0.001$, respectively). Separate examination of all the groups revealed similar positive correlation between HAM-D scores and TAS-20 scores.

The causality of this association between alexithymia and depression remains unclear. In other words, the question of whether alexithymia predisposes individuals to depression (the vulnerability hypothesis) or whether depression produces alexithymic symptoms is still controversial (6). Several studies have reported that the severity of depression mediates the association between alexithymia and suicidal behavior (30). However, more recent research has revealed that the connection between alexithymia and suicide persists even after the effect of depression has been eliminated (31). One long-term observational study has suggested that alexithymia is a significant predictor of subsequent suicidal ideation (32). A large part of previous studies supports the idea that alexithymia is more powerfully associated with suicidal ideation than suicidal behavior (29). Nonetheless, a few studies have reported a stronger link between alexithymia and suicidal behavior than with suicidal ideation (33). TAS-20 scores in the present study were lowest in the attempted suicide group and highest in the NSSI group. The difference was also statistically significant ($p= 0.008$). This picture may show that the individual embarks on behavior to concretize the difficulty in identifying and describing feelings and turns to self-injury as a form of expression, rather than suicide. This supports the hypothesis that individuals with difficulty in understanding their own emotional states may be less capable of identifying and applying strategies for tolerating stress or solving underlying problems in the short term and may therefore employ self- injury behavior to reduce disturbing arousal (34). Other factors may also be capable of affecting the relationship between alexithymia and suicide and NSSI. For example, there is evidence showing that low self-esteem, low social support levels, and attachment styles are separately associated with both the disposition to suicide and alexithymia (12).

Conclusion

The findings of this study show that the relationship between alexithymia and NSSI is stronger than those between alexithymia and suicidal ideation and attempted suicide. This reveals the need to evaluate alexithymia in individuals presenting due to self-injury behavior and ideation, and its critical importance in determining therapeutic strategies.

Limitations and future directions

Future research should concentrate on longitudinal studies detailing the association between alexithymia and NSSI and including its interaction with other variables. The limitation of our study is that we have insufficient number of patients and controls. It is possible to reach more generalizable data with studies with larger populations. We think that the data yielded by such studies will be useful in eliciting a better understanding of the relationship between alexithymia and emotion perception and in the application of more specific therapeutic approaches for the improvement of social skills in alexithymic individuals.

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Author Contributions:

Conception: S.Z., O.D., Data Collection and Processing: S.Z., O.D., Design: S.Z., O.D., H.U., Supervision: S.Z., O.D., Analysis and Interpretation: S.Z., Literature Review: S.Z., O.D., H.U Writer: S.Z., Critical Review: O.D., H.U.

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The data sets analyzed are available from the corresponding author.

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ORIGINAL ARTICLE

Comparison of Pica Prevalence Between Children and Adolescents with Iron Deficiency and Iron Deficiency Anaemia: A Prospective Cross-Sectional Study

Demir Eksikliği ve Demir Eksikliği Anemisi Olan Çocuklar ve Ergenler Arasındaki Pika Prevalansının Karşılaştırılması: Bir Prospektif Kesitsel Çalışma

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ABSTRACT

Background/Aims: The existing literature lacks comprehensive data on the association between the severity of iron deficiency (ID) and pica prevalence in children and adolescents. The aim of this study was to explore the prevalence of pica in apparently healthy children and adolescents, and to compare its occurrence between those diagnosed with ID and those with IDA.
Methods: This prospective cross-sectional study was conducted at the outpatient paediatric clinic over a period of three months. A total of 504 children and adolescents were enrolled in the study. Participants were categorized into three groups based on primary laboratory findings: Group 1 (healthy), Group 2 (isolated ID), and Group 3 (IDA).
Results: A pica prevalence rate of 5.35% was observed, with a significantly higher occurrence among children suffering from IDA compared to those with ID and their healthy counterparts (p: <0.0001). Moreover, the prevalence was significantly higher in the 12-17.9 years age group (p: 0.01). Female sex and serum ferritin level emerged as the most significant independent predictors associated with pica in our investigation.
Conclusions: Our study demonstrated a higher prevalence of the pica among children suffering from IDA, the most severe form of iron deficiencies, compared with those with isolated ID.

Keywords: Adolescent, children, iron deficiency, iron deficiency anaemia, pica

ÖZ

Arka Plan/Amaçlar: Mevcut literatürde demir eksikliğinin şiddeti (DE) ile çocuk ve ergenlerde pika prevalansı arasındaki ilişkiye dair kapsamlı veriler bulunmamaktadır. Bu çalışmanın amacı görünüşte sağlıklı çocuk ve ergenlerde pika prevalansını araştırmak ve DE tanısı alan kişiler ile DEA tanısı alan kişiler arasındaki görülme sıklığını karşılaştırmaktı.
Yöntemler: Bu prospektif kesitsel çalışma, pediatri polikliniğinde üç ay boyunca gerçekleştirildi. Çalışmaya toplam 504 çocuk ve ergen katılmıştır. Katılımcılar birincil laboratuvar bulgularına göre üç gruba ayrıldı: Grup 1 (sağlıklı), Grup 2 (izole DE) ve Grup 3 (DEA).
Bulgular: %5,35'lik bir pika yaygınlık oranı gözlendi; DEA'lı çocuklar arasında, DE'li çocuklar ve onların sağlıklı akranlarıyla karşılaştırıldığında önemli ölçüde daha yüksek bir görülme sıklığı gözlendi (p: <0,0001). Ayrıca 12-17,9 yaş grubunda prevalans anlamlı olarak daha yüksekti (p:0,01). Araştırmamızda kız cinsiyeti ve serum ferritin düzeyi pika ile ilişkili en önemli bağımsız belirleyiciler olarak ortaya çıktı.
Sonuçlar: Çalışmamız, demir eksikliğinin en şiddetli şekli olan DEA'dan mustarip çocuklarda, izole DE'li çocuklarla karşılaştırıldığında pika prevalansının daha yüksek olduğunu gösterdi.

Anahtar Kelimeler: ergen, çocuk, demir eksikliği, demir eksikliği anemisi, pika

Introduction

Iron deficiency (ID) stands as the predominant aetiology of nutritional anaemia on a global scale, posing a substantial public health challenge, particularly in developing regions (1). Epidemiological investigations have revealed a concerning prevalence of anaemia among children in these settings, with reports indicating that around one-third of preschool-aged children and half of those aged 5-15 years suffer from this condition (2,3). The spectrum of ID encompasses a continuum ranging from ID without anaemia to the more severe form known as IDA. ID without anaemia comprises two distinct stages: iron-deficient erythropoiesis, characterized by depleted iron stores and subsequent decreased transport iron, and iron depletion, denoting a reduction in stored iron levels. IDA represents the most severe manifestation of ID (4). Notably, iron plays a critical role in brain development, particularly in children, influencing various processes such as monoamine neurotransmitter function, myelination, as well as glial and neuronal energy metabolism (5). Iron deficiency anaemia (IDA) typically remains asymptomatic unless it reaches severe levels. 2 In instances where IDA manifests in early childhood, especially in severe and prolonged forms, it can lead to neurodevelopmental

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and cognitive impairments, which may not be entirely reversible despite the correction of the underlying IDA (2,6).

Pica is characterized by the recurrent consumption of non-nutritive and non-food substances outside the context of culturally normative practices or other mental or physical conditions lasting for a minimum duration of one month (7,8). The prevalence of pica exhibits variations among different populations, with reported frequencies showing discrepancies (9,10). Early diagnosis of pica can help prevent the complications it may cause (7).

The exact pathophysiological mechanisms of pica remain uncertain, despite numerous proposed aetiologies in the current medical literature. These proposed etiological factors include sensations of hunger, deficiencies in essential micronutrients such as iron, zinc, and calcium, gastrointestinal disturbances like dyspepsia, heightened family stress, and comorbid psychiatric conditions such as obsessive-compulsive disorder. Furthermore, a proclivity towards the taste and texture of non-nutritive substances ingested has been identified as a contributing factor (11,12). Although pica can manifest across all age groups, it is more commonly reported in children, individuals with mental retardation, those experiencing learning difficulties, and pregnant women. Notably, pica has been particularly associated with ID and IDA.

The observation that pica can occur even in the pre-anemic stage of ID in children and may serve as a valuable indicator for predicting ID is noteworthy. The intricate relationship between ID and pica remains incompletely elucidated, with studies suggesting bidirectional influences between the two conditions (8). The existing literature lacks comprehensive data on the association between the severity of ID and pica prevalence in children and adolescents, particularly in comparing isolated ID with IDA. This study aims to fill the gap in the literature by investigating the prevalence of pica in apparently healthy children and adolescents, comparing its occurrence between those diagnosed with isolated ID and IDA.

Material and Methods

Study design and sampling

The study design was approved by the Karatay University Ethics Committee under the approval number 2023/018, 17.11.2023. All participants gave informed consent. This prospective cross-sectional study was conducted at the outpatient paediatric clinic of Konya Beyhekim Training and Research Hospital, Turkiye, over a period of three months, from December 1, 2023, to March 1, 2024. Data pertaining to participants' application dates, sex, age, and laboratory parameters were extracted from the hospital's electronic information system.

Sample size calculation

The sample size for the current study was calculated based on an estimated pica prevalence of 12.3%, as reported in a previous study (13). Utilizing the G*Power 3.1.9.7 software, key parameters such as an alpha error of 5%, a difference of 10%, and a power level set at 80% were established. The calculated minimum required sample size based on these parameters was 504 children. The present study successfully enrolled a participant cohort that met the predetermined sample size threshold.

Inclusion criteria encompassed children and adolescents aged >2 to 17.9 years who were extensively queried about their pica history during the study period. Haemogram, serum iron, total iron binding capacity, and ferritin levels were assessed in all participants.

Exclusion criteria comprised children under 24 months, those with active infection, C-reactive protein levels >5 mg/dl, hemolytic anaemia, thalassemia, sickle cell disease, developmental delays, or neurological abnormalities such as autism spectrum disorders. Individuals with missing laboratory data were excluded.

Participants were categorized into three groups based on primary laboratory findings: Group 1 (healthy), Group 2 (isolated ID), and Group 3 (IDA). Age stratification included children aged >2–4.9 years, 5–11.9 years, and adolescents aged 12–17.9 years. Pica history was obtained from parents of preverbal children and directly from older children and adolescents, detailing episode durations and ingested substances, adhering to DSM-V criteria for diagnosis (14).

Laboratory investigations

Haemogram analysis was conducted using flow cytometric method on the Shenzhen Mindray Auto Haematology Analyzer BC-6800 (Shenzhen, China). Analysis of serum iron and total iron-binding capacity was performed through calorimetric assay using a commercial kit on the Shenzhen Mindray BS-2000M (Shenzhen, China). Serum ferritin level was determined using an immunoassay method with a commercial kit (ADVIA Centaur®) on the Siemens ADVIA Centaur® XPT (Siemens Diagnostics, Tarrytown, NY, USA).

The diagnosis of anaemia was based on the criteria established by the World Health Organization (WHO). Specifically, anaemia was defined as haemoglobin (Hb) levels below 11 g/dL for children aged 2.1-4.9 years, below 11.5 g/dL for children aged 5-11.9 years, below 12 g/dL for females aged 15 years and above, and below 13 g/dL for males aged 15 years and above. ID was identified as ferritin levels below 12.0 ng/mL for children aged 24-59 months and below 15 ng/mL in children aged 5-10 years and adolescents (15). IDA was characterized by the simultaneous presence of anaemia and low ferritin levels, as per age-specific thresholds, in the absence of any underlying conditions that could impact these parameters (16,17).

Statistical Analysis

Categorical variables were expressed as numerical values and percentages. The distribution of the parameters was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Given the non-normal distribution, all values were reported as median

Table 1. Comparison of Demographic Characteristics of Study Groups

	Healthy children (n:352)	Isolated iron deficiency (n:117)	Iron deficiency anaemia (n:35)	p-value			p-value€
Sex (Female/Male) (n, %)	188/164 (53.4/46.5)	69/48 (58.9/41.1)	29/6 (82.8/17.2)				
Age (years)	9.30 (6.8)	9.90 (10)	14 (10.1)	**0.034**§	G1-2 0.359	G2-3 0.104	G1-3 **0.009**
Pica (n, %)	6 (1.7)	5 (4.3)	16 (45.7)	**<0.0001***			
Pica duration (months)	6 (3)	2 (2.5)	24 (25.5) §	0.002	G1-2 0.082	G2-3 0.017	G1-3 **0.001**

Quantitative variables were presented as the median (IQR). Qualitative variables were expressed as number and percentages.

Results were compared using the Kruskal–Wallis test followed by the Bonferroni-corrected Mann–Whitney U test.

Significance was determined by p<0.05 for the Kruskal Wallis test and p<0.016 (p = 0.05/3) for the Bonferroni correction.

P-values with statistical significance were highlighted in bold.

Chi-square test were performed to compare categorical variables.

§Kruskal–Wallis test, € Mann–Whitney U test, *Chi-square test

G1-2: Healthy group versus isolated iron deficiency group

G2-3: Isolated iron deficiency group versus Iron deficiency anaemia group

G1-3: Healthy group versus Iron deficiency anaemia group

with interquartile range (IQR). The comparison of categorical variables across different groups was conducted using the chi-square test or Fisher's exact test. Group comparisons were made using the Mann-Whitney U test. The Kruskal-Wallis analysis of variance test was employed for group comparisons, and the Bonferroni corrected Mann–Whitney U-test was used for multiple comparisons. A significance level of p<0.05, or p<0.05/k for k comparisons was considered statistically significant. Forward stepwise multivariate logistic regression was applied to identify risk factors for pica. The statistical analysis was performed using the SPSS software package for Windows, version 21.0.

Results

Comparison of Demographic Characteristics of Study Groups

A total of 504 children and adolescents were enrolled in the study. Demographic analysis revealed a sex distribution of 43.3% males and 56.7% females, with ages ranging from >2 to 17.9 years and a median age of 9.85 years (IQR: 7.7, minimum-maximum 2.1-17.9 years). Upon sex-based analysis, it was observed that 24.1% of females exhibited isolated ID, with 10.1% experiencing IDA. In contrast, 22% of males showed isolated ID, with only 2.8% diagnosed with IDA. Statistical analysis revealed no significant difference in the prevalence of ID between males and females (p=0.579). However, a statistically significant discrepancy was noted in the occurrence of IDA, which was higher in females than in males (p: 0.001). A higher median age was found in the IDA group compared to the healthy group, with statistical significance observed in the comparison of median ages between the study groups (p: 0.009). Among all participants, 5.35% had a history of pica, with the group with IDA demonstrating a significantly longer duration of pica compared to the healthy group (p: 0.001). The prevalence of pica was statistically significantly higher in the IDA group than in the ID and healthy groups (p<0.0001) (Table 1).

Table 2. Comparison of the Isolated Iron Deficiency and Iron Deficiency Anaemia Rates According To Sex and Age Groups in the Study Population

Age groups		Healthy children			Isolated iron deficiency			Iron deficiency anaemia			p-value*
	Males	Females	Total	Males	Females	Total	Males	Females	Total	
>2-4.9 years (n, %)	33 (51.6)	31 (48.4)	64[a] (18.2)	18 (62.1)	11 (37.9)	29[a,b] (24.8)	3 (37.5)	5 (62.5)	8[a] (22.9)	<0.0001
5-11.9 years (n, %)	83 (45.4)	100 (54.6)	183[b] (52)	19 (48.7)	20 (51.3)	39[b] (33.3)	2 (50)	2 (50)	4[b] (11.4)	
12-17.9 years (n, %)	48 (45.7)	57 (54.3)	105[a] (29.8)	11 (22.4)	38 (77.6)	49[a] (41.9)	1 (4.3)	22 (95.7)	23[a] (65.7)	
Total (n, %)	164 (46.6)	188 (53.4)	352 (69.84)	48 (41)	69 (59)	117 (23.21)	6 (17.2)	29 (82.8)	35 (6.95)	

Qualitative variables were expressed as number and percentages. P-values with statistical significance were highlighted in bold.

*Chi-square test

Table 3. Comparison of Sex-Specific Frequency of Pica across Age Groups

Age groups				
	Males	**Females**	**Total**	p-value*
>2-4.9 years, n (%)	54 (53.5)	47 (46.5)	101	
Pica	4 (7.4)	6 (12.76)	10 (9.9)	0.368
5-11.9 years, n (%)	104 (46)	122 (54)	226	
Pica	1 (0.8)	4 (3.2)	5 (2.2)	0.238
12-17.9 years, n (%)	60 (33.9)	117 (66.1)	177	
Pica	0 (0)	12 (10.2)	12 (6.78)	**0.010**
Total, n (%)	218 (43.3)	286 (56.7)	504	
Pica	5 (2.29)	22 (7.69)	27 (5.35)	**0.008**

Quantitative variables were presented as the median (IQR). Qualitative variables were expressed as number and percentages.

Isolated Iron Deficiency and Iron Deficiency Anaemia Rates According To Sex and Age Groups in the Study Population

The reported frequencies of various pica types included coffee grounds in 2.18% of children, paper in 1.19%, soil in 0.99%, clay in 0.39%, both soil and clay in

Table 4. Comparison of Laboratory Characteristics of Study Groups

Characteristics	All participants	Healthy children	Isolated iron deficiency	Iron deficiency anaemia	p-value§	p-value€
Iron (ng/mL)	68 (51)	72 (40)	70 (53)	31 (45)	<0.0001	G1-2 0.737 G2-3 <**0.0001** G1-3 <**0.0001**
Total iron-binding capacity (µg/dL)	293 (85)	278 (80)	311.4 (79)	366 (78)	<0.0001	G1-2 <**0.0001** G2-3 <**0.0001** G1-3 <**0.0001**
Ferritin (ng/mL)	20.90 (19.70)	27 (20.60)	10.60 (4.10)	6 (8.15)	<0.0001	G1-2 <**0.0001** G2-3 0.051 G1-3 <**0.0001**
RBC (10^6/µL)	4.92 (0.51)	4.91 (0.52)	4.94 (0.47)	4.92 (0.70)	0.240	
Platelet count (10^3/µL)	324 (92)	322 (95)	324 (80)	337 (117)	0.306	
Haemoglobin (g/dL)	13.10 (9.90)	13.20 (1.60)	13.20 (1.40)	11.10 (0.70)	<0.0001	G1-2 0.256 G2-3<**0.0001** G1-3 <**0.0001**
Haematocrit (%)	38.60 (4.70)	38.60 (4.50)	39.30 (4.85)	35.0 (5.05)	<0.0001	G1-2 0.730 G2-3<**0.0001** G1-3 <**0.0001**
MCV (fL)	79 (6.50)	79.10 (6.90)	78.90 (6.25)	77.0 (10.75)	0.047	G1-2 0.478 G2-3 0.062 G1-3 **0.015**
MCH (pg)	26.80 (2.30)	27 (2.10)	26.70 (2.50)	24.90 (4.35)	<0.0001	G1-2 0.129 G2-3<**0.0001** G1-3 <**0.0001**
MCHC (g/dL)	33.90 (1.60)	34.10 (1.50)	33.90 (1.50)	32.20 (2.10)	<0.0001	G1-2 0.086 G2-3<**0.0001** G1-3 <**0.0001**
RDW (%)	13.50 (1.10)	13.30 (1.0)	13.70 (1.20)	14.60 (3.30)	<0.0001	**G1-2 0.001** G2-3 **0.002** G1-3 <**0.0001**
MPV (fL)	9.70 (1.70)	9.70 (1.65)	9.80 (1.50)	9.80 (1.95)	0.818	

Abbreviations: RBC: Red blood count, MCV: Mean corpuscular volume, MCH: Mean corpuscular haemoglobin, MCHC: Mean corpuscular haemoglobin concentration, RDW: Red blood cell distribution width, MPV: Mean platelet volume

Quantitative variables were presented as the median (IQR). Qualitative variables were expressed as number. Results were compared using the Kruskal–Wallis test followed by the Bonferroni-corrected Mann–Whitney U test. Significance was determined by p<0.05 for the Kruskal Wallis test and p<0.016 (p = 0.05/3) for the Bonferroni correction. P-values with statistical significance were highlighted in bold.

G1-2: Healthy group versus isolated iron deficiency group

G2-3: isolated iron deficiency group versus Iron deficiency anaemia group

G1-3: Healthy group versus Iron deficiency anaemia group

Table 5. Comparison of Demographic and Laboratory Characteristics of Pica and Non-Pica Groups

Characteristics	Pica group (n:27)	Non-Pica group (n:477)	p-value
Sex (Female/Male) (n, %)	22/5 (81.5/18.5)	264/213 (55.3/44.7)	**0.008** *
Age (years)	11.95 (11.9)	9.20 (7.8)	0.652
Iron (ng/mL)	64.50 (39)	70 (51)	0.352
Total iron-binding capacity (µg/dL)	312 (116)	292 (85)	0.123
Ferritin (ng/mL)	11.85 (10.80)	21.30 (19.80)	**<0.0001** €
RBC (10^6/µL)	4.71 (0.53)	4.93 (0.48)	**0.005** €
Platelet count (10^3/µL)	342.5 (141.5)	323 (91)	0.268
Haemoglobin (g/dL)	11.35 (1.32)	13.20 (1.70)	**<0.0001** €
Haematocrit (%)	36.75 (6.25)	38.60 (4.70)	**0.017** €
MCV (fL)	78.45 (6.37)	79.0 (6.70)	0.828
MCH (pg)	26.80 (2.58)	26.80 (2.20)	0.616
MCHC (g/dL)	33.75 (1.93)	34.0 (1.60)	0.075
RDW (%)	13.70 (1.57)	13.50 (1.10)	0.265
MPV (fL)	9.55 (2.30)	9.70 (1.50)	0.580

Abbreviations: RBC: Red blood count, MCV: Mean corpuscular volume, MCH: Mean corpuscular haemoglobin, MCHC: Mean corpuscular haemoglobin concentration, RDW: Red blood cell distribution width, MPV: Mean platelet volume

*Chi-square test, € Mann–Whitney U test

0.19%, napkin in 0.19%, and cigarette butts in 0.19%. The study population was categorized into age groups as follows: 20% in the >2-4.9 age group, 44.9% in the 5-11.9 age group, and 35.1% in the 12-17.9 age group. Of all participants, approximately 23% were classified under isolated ID, with 13.6% females and 9.4% males, while the IDA group comprised around 7% of participants, with 5.8% females and 1.2% males, with the rest forming the healthy control group. Adolescents exhibited a significantly higher prevalence of isolated ID and IDA compared to other age groups (p<0.0001) (Table 2).

Sex-Specific Frequency of Pica across Age Groups

Sex-wise analysis revealed a higher frequency of pica in females than males (p: 0.008). Although no significant sex-specific differences were observed across age groups, adolescent females demonstrated a significantly higher prevalence of pica compared to males (p: 0.010) (Table 3). A significant difference in pica prevalence was noted among the age groups, with the rates of 2% in the >2-4.9 years group, 1% in the 5-11.9 years group, and 2.4% in the 12-17.9 years group exhibiting a higher prevalence (p: 0.01).

Laboratory Characteristics of Study Groups

Significant disparities were noted among groups in terms of serum iron, total iron binding capacity, and ferritin levels (p<0.0001). The IDA group displayed lower

serum iron levels and higher total iron binding capacity compared to the healthy and isolated ID groups. Additionally, serum ferritin levels were significantly lower in both the isolated ID and IDA groups compared to the healthy group ($p<0.0001$). Significant differences were observed in haematological parameters such as haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and red cell distribution width (RDW) values among groups, with the IDA group demonstrating lower levels of haemoglobin, haematocrit, MCH, and MCHC, and higher RDW values compared to the isolated ID and healthy groups (Table 4). Additionally, individuals with pica exhibited statistically significant lower levels of serum ferritin, red blood cells (RBC), haemoglobin, and haematocrit compared to those without pica (Table 5).

Logistic regression of factors affecting pica

In the entire study cohort, a multiple regression analysis model was utilized to assess the variables that independently influenced pica. A multiple stepwise regression analysis was employed to elucidate the individual contributions of age, sex, serum ferritin level, haemoglobin, MCV, and RDW to the occurrence of pica. The results of the multivariate logistic regression analysis revealed that female sex ($\beta=2.767$, $p=0.047$, 95% Confidence Interval 1.015-7.544) and serum ferritin level ($\beta=0.919$, $p=0.001$, 95% Confidence Interval 0.875-0.965) emerged as the most significant independent predictors of pica in children.

Discussion

This study represents the first investigation in the literature to elucidate the relationship between the severity of ID and pica. Within our study cohort, a pica prevalence of 5.35% was observed, with a significantly higher occurrence among children suffering from IDA compared to those with ID and their healthy counterparts. Furthermore, a sex-based disparity in pica prevalence was statistically significant, with females exhibiting a higher prevalence than males. Notably, our findings revealed a markedly elevated prevalence of pica particularly among adolescent females. Female sex and serum ferritin level emerged as independent predictors of pica in our study. Moreover, the analysis indicated significantly lower levels of serum ferritin, RBC, haemoglobin, and haematocrit in the pica group compared to the non-pica group. This research, conducted in Konya within the Central Anatolian region of Turkiye, diverged from prior studies by highlighting coffee grounds as the predominant form of pica among children and adolescents in the region.

IDA demonstrates variable prevalence rates globally, contingent upon the level of development of individual countries. Reported prevalence rates of IDA in children range from 1.1% to 7.4% in the United States, 2-4% in Europe, and 64-71% in Africa (18,19). Since 2004, the Ministry of Health of the Republic of Turkiye has implemented iron supplementation from 4 months to 12 months of age. Despite two decades having passed since the inception of this initiative, ID persists in children over 24 months of age (20). According to a 2011 World Health Organization report, the prevalence of IDA among preschool children in Turkiye decreased from 32.5% to 30%. Limited studies in the past decade in Turkiye have focused on the prevalence of ID and IDA among children and adolescents. Previous investigations have shown variations in prevalence based on geographical location, methodologies, and age groups. Notably, studies encompassing infants under one year of age, during which IDA peaks, have reported higher prevalence rates. Across Turkiye, studies have reported ID prevalence ranging from 5.45% to 19.6%, with IDA prevalence varying from 1.4% to 30.1%. The prevalence of iron deficiency was 38.7% with IDA at 8.3% among school children in Aydın province(21), where females exhibited a higher rate of ID at 45.1% compared to males at 30.6%, and IDA rates were 11.6% in females and 4.1% in males, showing a significant sex-based difference, while a study in Samsun province(22), reported ID at 29.9% and IDA at 6.6% among children aged 7-14 years, and a study in Amasya province (23), found frequencies of ID at 26.2% and IDA at 13.1% in children aged 1-17 years, with higher rates of IDA observed in adolescent females. This study in Konya, Turkiye, represents the first investigation on the prevalence of ID, IDA, and pica among children and adolescents. Our findings revealed isolated ID in 23% of children and IDA in 7%. While the prevalence of ID and IDA in Konya was lower compared to previous studies, it was still noteworthy, with a significantly higher prevalence observed in females compared to males.

The prevalence of IDA in preschool-aged children, as reported by the WHO, stands at 27% (24). In our study, we found a 7.92% prevalence rate of IDA among children aged >2 to 4.9 years, with infants under 24 months excluded from the pica analysis. A recent systematic review, encompassing studies conducted in developing nations and focusing on children aged 10 and above, unveiled a variable prevalence range of IDA, spanning from 7.7% to 71.2% (1). In our study, the frequency of IDA among children aged 5 to 11.9 years was determined as 1.76%, with no significant sex-based differences observed. These findings indicate a notably lower prevalence of IDA in school-aged children compared to other age groups.

During adolescence, the increased iron requirement is attributed to rapid growth. Additionally, the onset of menstrual bleeding in females leads to a decrease in ferritin levels. The rising trend of irregular dietary habits and decreased consumption of iron-rich animal-based foods contribute to the development of IDA. Hence, the prevalence of IDA is higher in adolescent females (25-27). Globally, the exact prevalence of IDA among adolescents remains uncertain. In a study in the United States, approximately 17% of adolescent females were found to have ID, with 6% having IDA, while less than 1% of adolescent males showed ID. The WHO estimates that over 50% of females aged 12-15 in South-East Asia have anaemia, with no specific estimate available for males (28). A study in Nepal identified IDA in 6.86% of adolescent females and 5%

of adolescent males (29). In a retrospective study in Denizli province (25), the prevalence of IDA among adolescents was 3.3%, with the prevalence in females approximately 5 times higher than in males. Our study results indicated that children with IDA had a higher median age compared to the healthy control group. Furthermore, we observed a higher prevalence of IDA in females than in males. Consistent with the literature, our findings suggest that adolescent females are at a higher risk for IDA. Similarly, in our study, the prevalence of IDA in adolescent females was found 4.8 times higher than in males.

The aetiology of pica has been attributed to various factors; however, direct causality has not been established. The type and prevalence of pica consumed may vary depending on ethnic origin, geography, and socio-cultural factors. Additionally, factors such as the definition of pica in the study, the age group included in the study, and the participants' concealment of pica can influence the study results (30). Pica prevalence rates vary across different countries and age groups, with studies reporting rates of 12.3% in Germany13 among children aged 7-14, 6.7% in Iran (31) among children aged 6-15, 7.2% in Egypt (32) with an increasing prevalence with age, 30.7% in Sudan (33) among adolescent schoolchildren aged 10-19, and 3.8% in Switzerland7 among schoolchildren aged 7-13 using a clinical cut-off score of ≥4. The prevalence of pica in all participants in our study was found as 5.35%.

While studies on the prevalence of pica in children have been conducted in the literature, the number of studies specifically addressing pica in children with ID or IDA is limited. Some community-based studies have reported lower serum iron and ferritin levels in individuals with pica, suggesting a significant role of ID in the aetiology of pica (34). A previous meta-analysis has demonstrated a significant association between pica and low haemoglobin and haematocrit levels (35).

In our study, significant decreases in serum ferritin, haemoglobin, and haematocrit levels were observed in individuals with pica compared to those without. A study in Pakistan involving 862 children aged 2-6 with IDA reported a prevalence of pica at 37.2% (12). In our study, pica was identified in 45.7% of patients with IDA. Unlike previous studies, our research observed a higher prevalence of pica in older children and adolescents, with a significantly higher prevalence in females compared to males. Furthermore, individuals with IDA in our study had lower ferritin levels compared to those with isolated ID, and a significantly higher prevalence of pica was detected. Our study confirmed the previously established link between female sex and pica in Sudanese adolescents (33), identifying female sex and serum ferritin levels as independent predictors of pica in our cohort.

Serum ferritin serves as a reliable indicator of ID, with levels below 12 ng/mL strongly suggestive of ID (3). In our study, a decrease in ferritin levels was associated with 1.1 times increase in the likelihood of pica occurrence. Our findings demonstrated a relationship between the severity of ID and pica. Previous studies investigating pica prevalence in children with IDA noted that the prevalence of anaemia was moderate to severe, and the exclusion of adolescents from these studies may explain the higher prevalence of pica (12,36). In our study, most cases of IDA were mild, and adolescents, the age group with the highest prevalence of pica and IDA, were included.

Studies in the literature have indicated variations in pica prevalence based on sex (13,37). A recent study revealed that adolescent females had a 3.5 times higher risk of pica compared to males. Another study found a higher prevalence of geophagy in females compared to males (38). Similarly, in our study, the likelihood of pica occurrence in females was approximately 2.8 times more than in males. This finding may be attributed to the higher prevalence of IDA and pica in adolescent females in our study. The inclusion of infants or differences in study methodology in previous studies could also account for these discrepancies.

Pica, a condition characterized by the consumption of non-nutritive substances, has been linked to ID, with various substances such as clay, ice, starch, chalk, soap, paper, and raw rice being commonly ingested by individuals exhibiting pica behaviours (26). The relationship between pica and anaemia remains complex, with uncertainties regarding the causal direction of this association. Notably, pagophagia (ice consumption) has been strongly correlated with ID and has shown a greater response to iron therapy compared to other forms of pica, which have demonstrated varying degrees of efficacy in response to iron treatment (39,40). Among 120 children aged 2-10 with IDA and a history of pica in Pakistan, soil, sand, and lime were identified as the most common types of pica. Previous studies have highlighted soil consumption as the most common form of pica, accounting for 83% of cases in children with IDA in the South Eastern Anatolia region (41). In contrast to previous studies in Turkiye, our study identified coffee grounds as the most prevalent form of pica, which may be associated with the urban residence of patients visiting our clinic. Coffee ground pica has been predominantly reported in pregnant women rather than children in previous studies (42). Turkish coffee holds a significant cultural appeal in Turkish society, with its aroma being an enticing factor for individuals, potentially influencing those predisposed to pica behaviours towards coffee ground ingestion.

A limitation of our study was the lack of measurement of micronutrient concentrations such as zinc, calcium, and selenium. Additionally, the cross-sectional design of our study, which included patients admitted to the hospital, may not fully represent the general population. Nevertheless, the strengths of our study included a large sample size and the exclusion of children under the age of two.

Conclusions

Our study demonstrated a higher prevalence of pica in IDA, the most severe form of ID, compared to isolated ID. Female sex and serum ferritin levels were identified as independent variables associated with pica. Further prospective studies validating these results are warranted in this regard.

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Author contributions: SS and SKS study design. SS and SKS data collection. SS wrote the manuscript. All the authors have agreed to be accountable for all aspects of the study and have approved the final version of the manuscript.

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ORIGINAL ARTICLE

Effects of 3D Bone Models on Anatomy Education: Student Survey

3 Boyutlu Kemik Modellerinin Anatomi Eğitimine Etkileri: Öğrenci Anketi

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ABSTRACT

Background/Aim: Anatomy education is of great importance in evaluating the human body as a whole and understanding the normal functioning of organs and systems. Knowledge of human anatomy plays a critical role in the diagnosis of diseases, surgical interventions, evaluation of the health status of patients and interpretation of the results of advanced imaging techniques. This study aims to evaluate the satisfaction of learning anatomy with three-dimensional virtual anatomy atlas we developed, and to investigate the effect of virtual three-dimensional applications on learning compared to traditional materials.
Methods: The 3D applied atlas we developed was sent to the Faculty of Medicine Grade 1-2, Dentistry Grade 1, and Physiotherapy and Rehabilitation Grade 1 students. Students were asked to use the 3D applied atlas in addition to traditional medical education materials in their anatomy learning process. A 9-question Google Forms survey was prepared to evaluate their satisfaction of the application.
Results: 471 participants from the Faculty of Dentistry, Medicine Grade 1-2, and Physiotherapy Rehabilitation classes participated in our survey. Of the participants, 140 were Faculty of Dentis-try students, 70 were Physical Therapy and Rehabilitation (PTR), 172 were Faculty of Medicine 1st grade and 89 were Faculty of Medicine 2nd grade. The number of students who found two-dimensional atlases useful was 198, while the number of students who found 3D models useful was 231. The number of students who found the cadaver model useful was 161.
Conclusion: Based on the survey data we obtained, we can say that the students are satisfied with our 3D atlas application and have a positive attitude towards three-dimensional educational materials.

Keywords: Anatomy education, Anatomy atlas, 3D anatomy, bone anatomy

ÖZ

Amaç: Anatomi eğitimi, insan vücudunu bir bütün şeklinde değerlendirmek, organ ve sistemlerin normal işleyişini özümsemek açısından büyük bir öneme sahiptir. Hastalıkların teşhisinde, cerrahi müdahalelerde, hastaların sağlık durumlarının değerlendirilmesinde, ileri görüntüleme teknikle-rinin sonuçlarının yorumlanmasında; insan anatomisinin bilinmesi kritik bir rol oynamaktadır. Bu çalışma, geliştirdiğimiz üç boyutlu sanal anatomi atlasının anatomi öğrenme konusundaki mem-nuniyeti değerlendirmeyi ve geleneksel materyallere kıyasla sanal üç boyutlu uygulamaların öğrenmeye etkisini araştırmayı amaçlamaktadır.
Metod: Geliştirdiğimiz 3D uygulamalı atlas, dönemin başında Tıp Fakültesi Dönem 1-2,,Diş Hekimliği Dönem 1 ve Fizyoterapi ve Rehabilitasyon Dönem 1 öğrencilerine gönderildi. Öğren-cilerin, anatomiyi öğrenme süreçlerinde geleneksel tıp eğitimi materyallerine ek olarak 3D uygu-lamalı atlası da kullanmaları istendi. Uygulamanın memnuniyetinin değerlendirilebilmesi için 9 soruluk bir Google forms anketi hazırlandı.
Bulgular: Anketimize; Diş Hekimliği, Tıp Dönem1-2 ve Fizyoterapi Rehabilitasyon sınıflarından toplam 471 kişi katıldı. Katılımcıların 140'ı Diş Hekimliği Fakültesi, 70'i Fizik Tedavi ve Rehabili-tasyon (FTR), 172'si Tıp Fakültesi 1. Dönem ve 89'u Tıp Fakültesi 2. Dönem öğrencisiydi. İki boyutlu atlas kullanımını faydalı bulan öğrenci sayısı 198, 3 boyutlu modelleri faydalı bulan öğrenci sayısı ise 231 oldu. Kadavra modelini faydalı bulan öğrenci sayısı ise 161 oldu.
Sonuç: Elde ettiğimiz anket verileri doğrultusunda, öğrencilerin 3D atlas uygulamamızdan mem-nun kaldıklarını, üç boyutlu eğitim materyallerine olumlu yaklaştıklarını söyleyebiliriz.

Anahtar Kelimeler: Anatomi eğitimi, Anatomi atlası, 3D anatomi, Kemik anatomisi

Introduction

Anatomy is the science that studies the structural features of organisms and the location, size and shape of their organs. Anatomy education is essential in evaluating the human body and understanding the normal functioning of organs and systems. Anatomy education should be provided in the most understandable way, especially in medical faculties and faculties that train qualified personnel for human health professions such as dentistry, physiotherapy and rehabilitation. Knowledge of human anatomy plays a critical role in the diagnosis of diseases, surgical interventions, evaluation of the health status of patients and interpretation of the results of advanced imaging techniques (1).

Two-dimensional atlases, three-dimensional anatomical body models made of plastic or wooden materials, and cadavers are frequently used materials in anatomy education. Cadaver dissections are especially useful for enriching three-dimensional thinking. However,

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today, alternative methods have been sought due to the difficulties in obtaining cadavers and the students' access to educational materials outside the laboratory environment (2,3). During the COVID-19 pandemic period, with the necessity of student education to evolve into distance education, students who were away from laboratories could not conceptualize anatomical structures with classical methods in online education. This made establishing a good anatomy basis difficult and created deficiencies in integrating information in the clinical approach (4). Situations such as the limited time students spend in laboratories and insufficient existing materials also reveal the necessity of new methods in anatomy education. Some countries (United Kingdom and France) have shortened the time spent on anatomy courses to reduce the burden on medical education, resulting in the inadequacy of traditional teaching materials. Therefore, the need for different learning methods to increase learning efficiency has emerged (5-7).

Three-dimensional imaging of anatomical structures has improved with developing technology. Interactive computer programs and virtual simulations are increasingly used in anatomy education. Three-dimensional anatomy atlases and applications integrated with virtual reality (or augmented reality) facilitate understanding anatomical structures, especially incredibly complex and smaller ones. It is argued that they contribute more to understanding the relationships of organs and other formations with each other and the locations of these structures. In addition, students can access educational materials outside the laboratory environments thanks to these applications, which can be easily accessed through smart phones, tablets, or computers (8).

This study aims to evaluate the satisfaction of the three-dimensional virtual anatomy atlas we developed with the anatomy learning of the students of the Faculty of Medicine, Dentistry, Physiotherapy and Rehabilitation, where we teach skeletal system anatomy, and to investigate the effect of virtual three-dimensional applications on learning compared to traditional materials.

Material and Methods

Computed Tomography (CT) images obtained retrospectively from Selcuk University Faculty of Medicine, Department of Radiology, were turned into 3D models using the Mimics Basic application in the computer environment. For the 3D modeled bones, the structures of anatomical importance were given a color using the Map-Texture technique. The application interface and texts were prepared in Turkish, paying attention to anatomical terminology. Firstly, 3D modeling of the humerus, radius, ulna, and scapula, which are the junction bones of the upper extremity, and the sternum bones of the torso skeleton, were made (Figure 1).

The names of the anatomical formations on the bone were explained under the heading 'teorik' (theoretical in English) and the information about these formations under the heading 'pratik' (practical in English). The information in the practical section was designed to be audible so that students could listen (Figure 2).

Ten questions were added to our 3D atlas application so that students can evaluate their achievements (Figure 3).

The 3D applied atlas we developed was sent to the Faculty of Medicine Grade 1-2, Dentistry Grade 1, and Physiotherapy and Rehabilitation Grade 1 students at the beginning of the semester. Students were asked to use the 3D applied atlas in addition to traditional medical education materials in their anatomy learning process. A 9-item Google Forms survey was prepared to evaluate their satisfaction of the application. After students completed the bone education, survey forms were sent online. Since participation in the survey was voluntary, a consent form was added to indicate whether students agreed to participate (Figure 4).

The nine questions we asked to be evaluated in the survey were as follows:

Question 1 (Q1). I benefited from anatomy atlases for the anatomy course.

Question 2 (Q2). I benefited from applications containing 3D models for the anatomy course.

Question 3 (Q3). 3D bone models were effective in learning the anatomy course.

Question 4 (Q4). 3D bone models strengthened my visual memory.

Question 5 (Q5). 3D bone models were effective in improving my clinical knowledge.

Question 6 (Q6). 3D bone models were effective in learning anatomical terms.

Question 7 (Q7). 3D bone models helped me compare similar formations in different bones.

Question 8 (Q8). 3D bone models were as useful as ready-made bone models.

Question 9 (Q9). Cadaver courses were effective for my anatomy education.

The students were asked to rate the questions on a scale of 1 to 5: 1- Strongly disagree, 2 - Disagree, 3 - Undecided, 4 - Agree, 5 - Strongly agree.

Statistical Analysis

Data obtained from Google Forms was transferred to the Microsoft Excel table. Statistical analyses were performed using the SPSS 27.0 (IBM Inc, Chicago, IL, USA) program. Descriptive statistics of the numerical and categorical data were analyzed and numerical

parameters were expressed as quartiles, median (min-max), and categorical variables were expressed as frequency and percentage. Kolmogrov-Smirnov test, histogram analysis, and skewness/kurtosis data were used to evaluate the suitability of numerical or ordinal variables for normal distribution. Mann-Witney U test was employed to compare two independent groups. Intergroup relationships were compared with the Kruskal-Wallis H test in multiple group comparisons. Bonferroni correction was performed during pairwise comparisons with post hoc analysis. Internal reliability analysis was utilized for the appropriate survey questions, and Cronbach's alpha value was calculated. Pearson chi-square analysis was used to analyze the relationship between binary categorical groups. The correlations between the survey questions were evaluated using Spearman correlation analysis. In the study, the type-I error rate was taken as 5%, and a p-value of <0.05 was considered significant.

Results

A total of 471 participants from the Faculty of Dentistry, Medicine Grade 1-2, and Physiotherapy Rehabilitation classes participated in our survey. Of the participants, 140 were Faculty of Dentistry students, 70 were Physical Therapy and Rehabilitation (PTR) students, 172 were Faculty of Medicine 1st Grade students, and 89 were Faculty of Medicine 2nd Grade students. The class distribution of the participating students is shown in Table 1.

61.8% of the students participating in the survey were female (291 people) and 38.2% were male (180 people).

Table 2 shows the answers given by the students who participated in the survey. Questions 2-8 were related to 3D modeling. Cronbach's analysis of the answers to these questions checked internal reliability. It was determined that the answers to questions 2-8 were consistent with each other. This indicated the reliability of the answers to our survey questions (Cronbach's a = 0.956).

When the answers of the surveyed students were compared according to their gender, there was no significant difference (all p values >0.05) (Table 3).

As a result of comparing the survey answers according to classes, there was a statistically significant difference between the answers given by the Faculty of Dentistry students and the answers given by the Faculty of Medicine Grade 1 students for the 3rd question (p = 0.004). Accordingly, 3D bone models were found to be more useful in teaching anatomy courses by Faculty of Dentistry students than Faculty of Medicine Grade 1 students. 3-dimensional bone models were found significantly more successful in strengthening visual memory by Faculty of Dentistry students than Faculty of Medicine Grade 1 students (p=0.012). 3D bone models significantly improved clinical knowledge in Dentistry and PTR students than in Faculty of Medicine Grade 1 students (p<0.05). PTR students found 3D bone models as useful as ready-made ones compared to Faculty of Medicine Grade 1 students (p<0.05). The comparison of all questions according to classes is given in tables and diagrams (Table 4) (Figures 5-9).

There was a moderate and strong positive correlation between all survey questions. There was a moderate and low consistent positive correlation between questions 1-2-9. The correlations between questions are given in Table 5.

The number of students who found two-dimensional atlases useful was 198, while the number of students who found 3D models useful was 231. The number of students who found the cadaver model useful was 161. The distribution of the other answers given by the participants is given as a heat map (Tables 6,7).

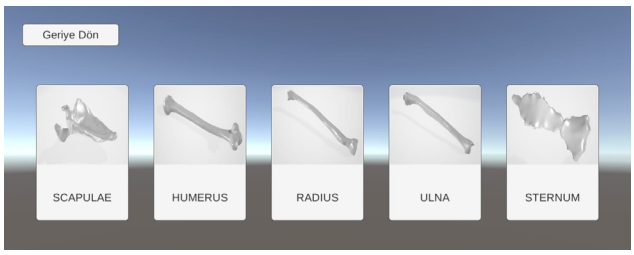

Figure 1. 3D modeled atlas images of scapulae, humerus, radius, ulna and sternum.

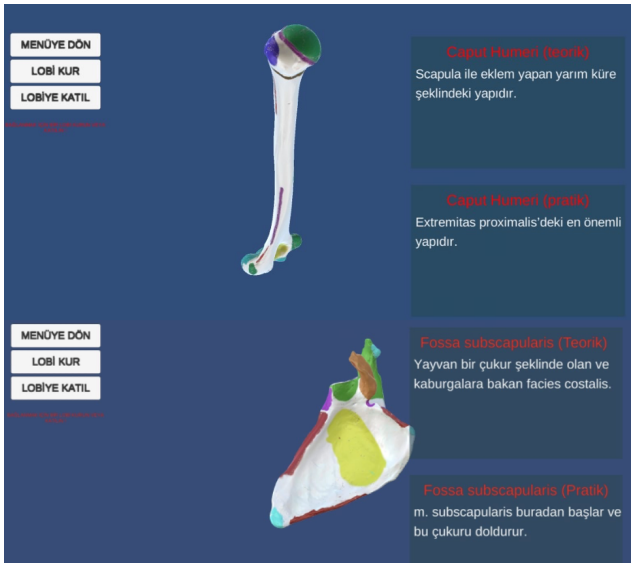

Figure 2. Representation of each of the anatomical formations in bones with different colors of paint and images of theoretical and practical information about these formations.

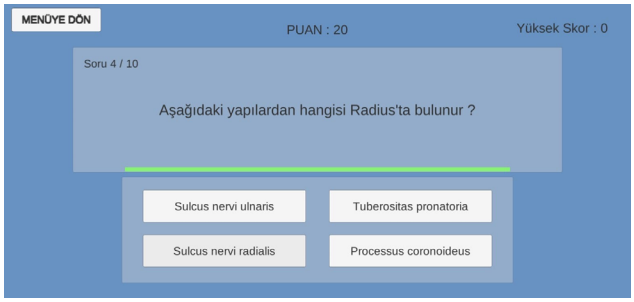

Figure 3. An example of questions in the application.

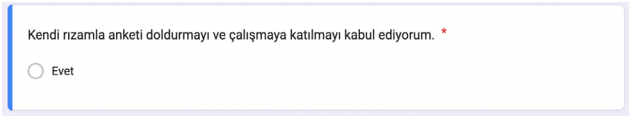

Figure 4. Image showing students' willingness to participate in the survey.

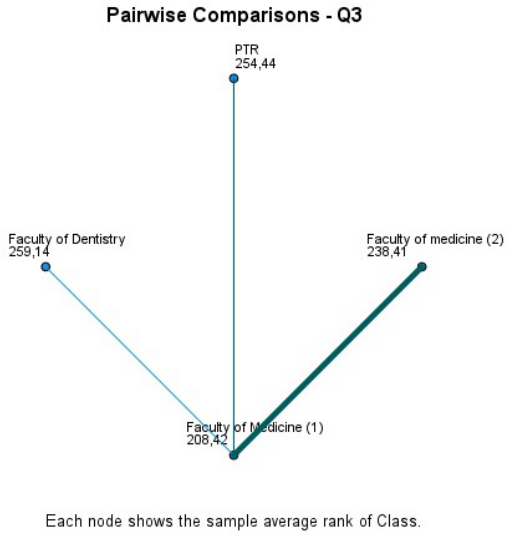

Figure 5. Comparison of Question 3 by binary classes and summary diagram of weight scores. The diagram shows the degree of significance from darker to lighter colors. The lightest colored line reflects a significant difference.

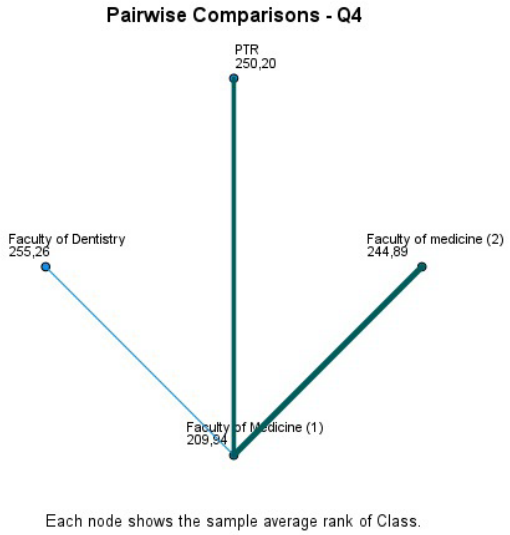

Figure 6. Comparison of Question 4 by binary classes and summary diagram of weight scores. The diagram shows the degree of significance from darker to lighter colors. The lightest colored line reflects a significant difference.

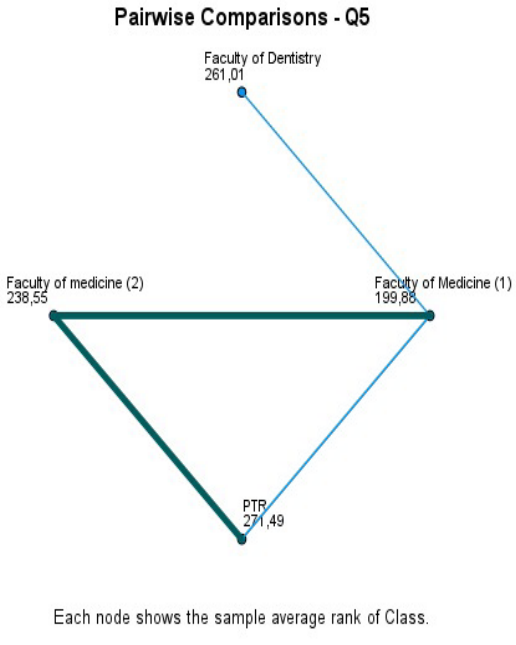

Figure 7. Comparison of Question 5 by binary classes and summary diagram of weight scores. The diagram shows the degree of significance from darker to lighter colors. The lightest colored line reflects a significant difference.

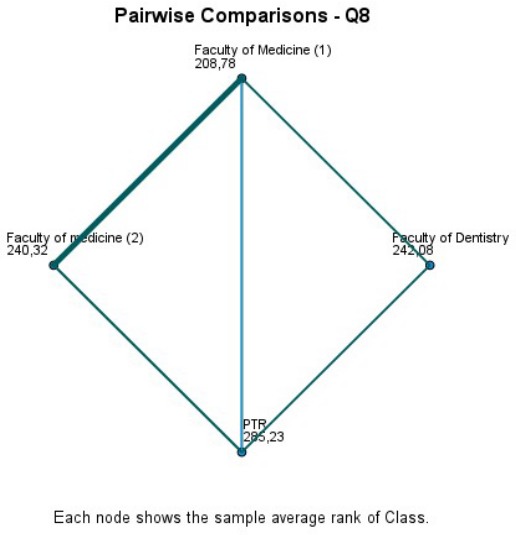

Figure 8. Comparison of Question 8 by binary classes and summary diagram of weight scores. The diagram shows the degree of significance from darker to lighter colors. The lightest colored line reflects a significant difference.

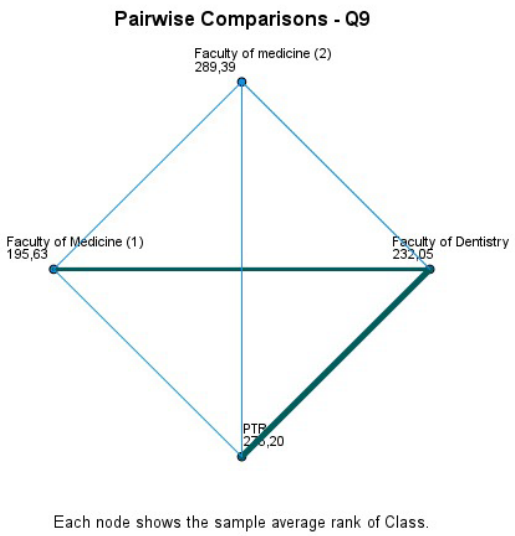

Figure 9. Comparison of Question 9 by binary classes and summary diagram of weight scores. The diagram shows the degree of significance from darker to lighter colors. The lightest colored line reflects a significant difference.

Table 1. Class distribution of the students participating in the survey.

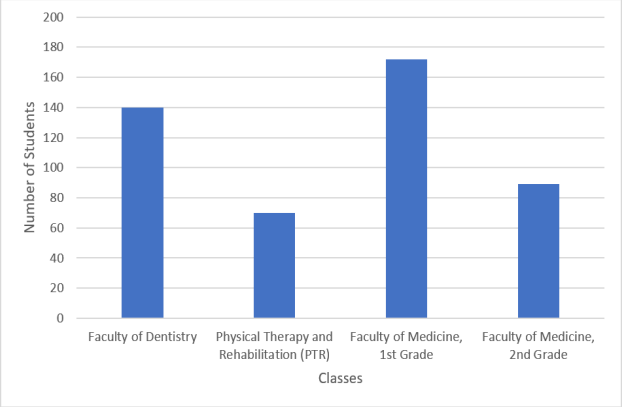

Table 3. Comparison of survey answers by gender in the general sample.

	Gender		P
Evaluation	Female	Male	
Question 1	3 (1-5)	3 (1-5)	0.212
Question 2	3 (1-5)	3 (1-5)	0.706
Question 3	4 (1-5)	4 (1-5)	0.185
Question 4	4 (1-5)	4 (1-5)	0.182
Question 5	4 (1-5)	3 (1-5)	0.074
Question 6	4 (1-5)	3 (1-5)	0.546
Question 7	3 (1-5)	4 (1-5)	0.911
Question 8	3 (1-5)	3 (1-5)	0.457
Question 9	3 (1-5)	3 (1-5)	0.50

**Ordinal data are expressed as IQR (quartiles [median, min-max]).*

Table 2. Distribution of answers according to the survey results.

Evaluation	Answer	N(%)	Evaluation	Answer	N(%)
Question 1	Strongly disagree	77 (%16.3)	**Question 6***	Strongly disagree	39 (%8.3)
	Disagree	86 (%18.3)		Disagree	52 (%11)
	Undecided	110 (%23.4)		Undecided	142 (%30.1)
	Agree	118 (%25.1)		Agree	142 (%30.1)
	Strongly agree	80 (%17)		Strongly agree	96 (%20 .4)
Question 2*	Strongly disagree	57 (%12.1)	**Question 7***	Strongly disagree	43 (%9.1)
	Disagree	70 (%14.9)		Disagree	69 (%14.6)
	Undecided	113 (%24)		Undecided	124 (%26.3)
	Agree	132 (%28)		Agree	140 (%29.7)
	Strongly agree	99 (%21)		Strongly agree	95 (%20 .2)
Question 3*	Strongly disagree	39 (%8.3)	**Question 8***	Strongly disagree	45 (%9.6)
	Disagree	50 (%10.6)		Disagree	76 (%16.1)
	Undecided	117 (%24.8)		Undecided	136 (%28.9)
	Agree	152 (%32.3)		Agree	135 (%28.7)
	Strongly agree	113 (%24)		Strongly agree	79 (%16.8)
Question 4*	Strongly disagree	40 (%8.5)	Question 9	Strongly disagree	112 (%23.8)
	Disagree	49 (%10.4)		Disagree	48 (%10.2)
	Undecided	111 (%23.6)		Undecided	150 (%31.8)
	Agree.	158 (%33.5)		Agree	87 (%18.5)
	Strongly agree	113 (%24)		Strongly agree	74 (%15,7)
Question 5*	Strongly disagree	43 (%9.1)			
	Disagree	69 (%14.6)			
	Undecided	129 (%27.4)			
	Agree	140 (%29.7)			
	Strongly agree	90 (%19.1)			

**Internal reliability analysis was conducted for the 3D model evaluation questions (for questions 2-8). and Cronbach's α = 0.956*

Table 4. Comparison of survey answers by classes.

	Class				P
Evaluation	Dentistry	PTR	Faculty of Medicine 1st Grade	Faculty of Medicine 2nd Grade	
Question 1	3 (1-5)	3 (1-5)	3 (1-5)	3 (1-5)	0,073
Question 2	4 (1-5)	4 (1-5)	3 (1-5)	4 (1-5)	0,053
Question 3	4 (1-5) [b]	4 (1-5)	3 (1-5) [a]	4 (1-5)	0,004
Question 4	4 (1-5) [b]	4 (1-5)	4 (1-5) [a]	4 (1-5)	0,012
Question 5	4 (1-5) [b]	4 (1-5) [c]	3 (1-5) [a, d]	4 (1-5)	<0,001
Question 6	4 (1-5)	3 (1-5)	3 (1-5)	4 (1-5)	0,068
Question 7	4 (1-5)	3 (1-5)	3 (1-5)	4 (1-5)	0,129
Question 8	3 (1-5)	4 (1-5) [b]	3 (1-5) [a]	3 (1-5)	0,001
Question 9	3 (1-5)	3 (1-5) [a,f]	3 (1-5) [b,c]	4 (1-5) [d,e]	<0,001

**Ordinal data are expressed as IQR (quartiles [median, min-max]).*

**Bonferroni correction was performed and compared in pairwise comparison. Paired signs (a-b), (c-d) and (e-f) indicate the classes where significant differences were observed.*

Table 5. Examination of correlation directions and correlation strengths between survey questions

		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Question 9
Question 1	rho		0.590	0.572	0.526	0.503	0.510	0.552	0.512	0.456
	P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Question 2	rho	0.590	1.000	0.707	0.693	0.628	0.659	0.660	0.604	0.443
	P	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Question 3	rho	0.572	0.707		0.876	0.769	0.790	0.781	0.725	0.464
	P	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Question 4	rho	0.526	0.693	0.876		0.764	0.811	0.788	0.686	0.449
	P	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001
Question 5	rho	0.503	0.628	0.769	0.764		0.811	0.793	0.733	0.522
	P	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001
Question 6	rho	0.510	0.659	0.790	0.811	0.811		0.828	0.733	0.464
	P	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001
Question 7	rho	0.552	0.660	0.781	0.788	0.793	0.828		0.773	0.516
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001
Question 8	rho	0.512	0.604	0.725	0.686	0.733	0.733	0.773		0.522
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001
Question 9	rho	0.456	0.443	0.464	0.449	0.522	0.464	0.516	0.522	
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

Table 6. Cross-tabulation relationship between Questions 1 and 2 and heat map of answers

		I benefited from applications containing 3D models					Total
Strongly disagree		**Disagree**	**Undecided**	**Agree**	**Strongly agree**		
I benefited from anatomy atlases for the anatomy course	Strongly disagree	34	17	12	6	8	77
	Disagree	13	26	25	15	7	86
	Undecided	4	20	51	22	13	110
	Agree	5	5	21	72	15	118
	Strongly agree	1	2	4	17	56	80
Total		57	70	113	132	99	471

Table 7. Cross-tabulation relationship between Questions 2 and 9 and heat map of answers

		Cadaver courses were effective for my anatomy education					Total
Strongly disagree		Disagree	Undecided	Agree	Strongly agree		
I benefited from applications containing 3D models	Strongly disagree	34	8	8	2	5	57
	Disagree	20	22	18	2	8	70
	Undecided	29	7	50	19	8	113
	Agree	21	5	49	46	11	132
	Strongly agree	8	6	25	18	42	99
Total		112	48	150	87	74	471

Discussion

In anatomy learning, in addition to traditional methods such as two-dimensional atlases, two-dimensional PowerPoint presentations, and books, three-dimensional anatomical body models and cadavers are used to add dimension to thinking. However, today, virtual applications and environments with augmented reality, such as three-dimensional atlases, are also being used to support learning. Therefore, instructors have recently conducted many studies investigating which methods students are satisfied with (8). We conducted a satisfaction survey with four classes studying anatomy at our university to understand the benefits of the 3D atlas model we developed for students. According to the results we obtained from our study, a high percentage (52%) of Medicine, Dentistry, and Physiotherapy Rehabilitation students were satisfied with the 3D atlas application. 42.1% were satisfied with two-dimensional atlas learning, and 34.2% with cadaver training. Examining these results, we can deduce that students are willing to use 3D applications in addition to traditional materials. Like our study, Martin G. et al. presented students with two-dimensional presentations and three-dimensional applications about upper extremity muscles and then distributed a satisfaction survey. Students were mostly satisfied with the three-dimensional application (9). A study conducted with 49 Dentistry students in Pakistan investigated the effect of two-dimensional presentations and 3D anatomy atlases on students' academic performance. It was found that the academic success of the group trained using 3D atlases was higher. It was argued that retention of anatomical information learned through 3D atlases increases in the short and long term (4). De Faria et al. compared the virtual and stereoscopic anatomy education model between groups in neuroanatomy education. They stated that this model encouraged knowledge development and was more effective in learning (10).

Contrary to these studies, Donnelly et al. randomly divided the faculty of medicine Grade 1 students into two groups and exposed one group to the projection containing dissection materials and the other to the virtual human dissector application. They conducted an exam to evaluate the learning level between the two groups. Since the exam results were similar between the two groups, they argued that the virtual human dissector application could be used as an alternative to traditional education methods. However, it was not more effective in learning (11).

According to our survey, 57.5% of students gave feedback that the 3D Atlas application improved their visual memory. The number of Dentistry students who thought their visual memory had improved was significantly higher than the number of faculty of Medicine Grade 1 students. Although there was a higher number of positive feedback from dentistry students than the other two classes, there was no significant difference between them. Eroğlu et al. compared students' ability to retain information in the short and long term by using 3D PDF and 2D atlas materials. They concluded that using three-dimensional materials for organs with complex anatomy was more beneficial and learning was more memorable in the short and long term (12).

Although three-dimensional educational materials facilitate comprehension, some studies in which students were tested suggested that the use of both two-dimensional and three-dimensional learning materials did not create a statistically significant difference in the exam results (13).

The contribution of 3D anatomy atlases to clinical knowledge is also controversial in the literature, as it is pretty complex to investigate the relationship between anatomy education and professional practices. In professional practice, the ability to internalize the information and use it effectively in practice is as important as the adequacy of the theoretical education received. This suggests that individual differences should also be considered (14,15). In our survey, 230 students (48.8%) reported that our 3D Atlas application contributed to their clinical knowledge. It can be said that dentistry and PTR students especially benefit from 3D atlases in improving their clinical skills. According to the data obtained from a survey study conducted on new specialists to investigate the effect of anatomy knowledge on clinical performance, almost half of the participants gave feedback that they did not receive adequate anatomy education (16). This makes it questionable how well traditional learning methods work in clinical integration. Increasing concerns about the inadequacy of traditional materials have also encouraged the development of new learning models (17).

Judit Beerman et al. showed the complex liver surgical anatomy with two-dimensional and three-dimensional materials to 4th and 5th-grade medicine students and then distributed questions for them to answer. The results reported that men benefited significantly more from 3D presentations than women (18). In our study, there was no significant difference between the survey answers of men and women who participated in the survey.

As a result, in line with the survey data we obtained, the students are satisfied with our 3D atlas application and have a positive attitude towards three-dimensional educational materials. It is also clear that students in education still request two-dimensional atlas and cadaver materials. Therefore, we can conclude that the use of three-dimensional educational materials in a way that supports traditional materials will help students develop more comprehensive thinking skills in the clinic and facilitate the understanding of anatomical formations, especially those with more complex structures. For this reason, developing our 3D anatomy atlas by converting the images obtained

from cadavers into 3D images to include all body systems will increase its contribution to the clinical training of students. It would be useful for academician to use three-dimensional materials in addition to two-dimensional PowerPoint presentations to deepen two-dimensional perception and improve the ability of the brain to perceive while creating course materials.

Declarations

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ORIGINAL ARTICLE

Evaluation of Stroke Patients Diagnosed with Rheumatologic Diseases

İnme Geçiren Romatolojik Hastalık Tanılı Hastaların Değerlendirilmesi

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ABSTRACT

Objectives: Some comorbid diseases are recognized as specific risk factors for stroke. Rheumatological diseases constitute an important group of these diseases. In our study, we evaluated patients who were followed up for stroke in our clinic. We included patients with additional rheumatological diagnoses in a separate group and attempted to determine their differences from patients without a diagnosis. In this way, we aimed to investigate the effect of rheumatological comorbidity on prognosis in stroke patients.
Material and methods: In the study, we included patients who were admitted to our hospital between 2016-2020, and diagnosed with ischemic stroke, hemorrhagic stroke, transient ischemic attack, hemorrhagic infarction, and were hospitalized. Age, gender, stroke subtype, need for intensive care and exitus status of these patients were recorded. We compared patients with a rheumatological diagnosis to patients with other stroke diagnoses using appropriate statistical methods.
Results: 2053 patients with an average age of 66.22±14.33 participated in the study. A total of 37 patients were diagnosed with at least 1 rheumatological disease. We calculated the average age of these patients as 51.62±15.88. Compared to patients without a diagnosis of rheumatological disease, the age was significantly lower($p<0.001$). However, we did not find a significant relationship between the distribution of stroke subtypes($p=0.538$), and there was no significant difference in terms of gender($p=0.149$). No statistical significance was observed in intensive care unit admissions and exitus rates. ($p=0.384,0.868$)
Conclusion: Some rheumatologic diseases are known to be linked to stroke risk. In our study, we did not observe a significant difference between the groups in terms of prognosis. Having a history of stroke is an independent risk factor for developing stroke in the future. We believe that since patients with a rheumatological diagnosis have a stroke at a younger age, their risk of a subsequent stroke increases, and their follow-up should be more frequent.

Keywords: Neurology, Rheumatological diseases, Stroke, Ischemic stroke

ÖZ

Amaç: Komorbid hastalıkların bazılarının inme için özellikle risk faktörü olduğu bilinmektedir. Bu hastalıklar içinde önemli bir grubu da romatolojik hastalıklar oluşturmaktadır. Çalışmamızda kliniğimizde inme nedeni ile takip edilen hastalar değerlendirilmiş ek romatolojik tanısı bulunan hastalar ayrı bir gruba alınarak tanısı olmayan hastalardan farklılıkları saptanmaya çalışılmıştır. Bu sayede inme hastalarında romatolojik komorbiditenin prognoz üzerine etkisini araştırmayı amaçlıyoruz.
Gereç ve Yöntem: Çalışmaya 2016-2020 tarihleri arasında hastanemize başvuran ve yatırılarak takip edilen iskemik inme, hemorajik inme, geçici iskemik atak, hemorajik enfarkt tanılı hastalar dahil edildi. Bu hastaların yaş, cinsiyet, inme alttipi, komorbid hastalık alttipi, yoğun bakım ihtiyacı, exitus durumları kayıt altına alındı. Romatolojik tanıya sahip olan hastalar diğer inme tanılı hastalarla uygun istatistiksel yöntemler kullanılarak karşılaştırıldı.
Bulgular: Çalışmaya yaş ortalaması 66.22±14.33 olan 2053 hasta katıldı. Bu hastaların 37 tanesinde en az 1 romatolojik hastalık tanısı bulunmaktaydı. Bu hastaların yaş ortalaması 51.62±15.88 olarak hesaplandı. Romatolojik hastalık tanısı bulunmayan hastalarla kıyaslandığında yaş anlamlı olarak daha düşük izlendi ($p<0.001$). Ancak inme alttiplerinin dağılımı açısından anlamlı ilişki yoktu($p=0.538$), cinsiyetler açısından anlamlı farklılık izlenmedi($p=0.149$). Yoğun bakım yatışları ve exitus oranları arasında istatistiksel anlamlılık yoktu ($p=0.384,0.868$).
Sonuç: Bazı romatolojik hastalıkların inme için risk faktörü olduğu bilinmektedir. Çalışmamızda prognoz açısından gruplar arası belirgin farklılık izlenmedi. Bu nedenle romatolojik tanısı bulunan hastaların inme prognozu genel popülasyonla benzer olarak değerlendirilebilir. Geçmişinde inme öyküsü olması gelecekte inme gelişmesi açısında bağımsız bir risk faktörüdür. Romatolojik tanısı bulunan hastaların daha genç yaşta inme geçirmeleri nedeniyle bir sonraki inme açısından riskleri artmakta ve takiplerinin daha sık olması gerektiği kanaatindeyiz.

Anahtar Kelimeler: nöroloji, romatolojik hastalıklar, inme, iskemik inme

Introduction

Stroke is one of the most common causes of mortality and morbidity worldwide. It is known that many modifiable and unchangeable conditions contribute to its etiology. Some modifiable factors include comorbid diseases. The most important risk factor is age (1). However, rheumatologic diseases should also be considered and investigated, especially in strokes that develop at a young age (2). In the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of ischemic strokes, large vessel atherosclerosis, which are common causes of stroke, strokes of cardiac origin, and strokes that are not caused by lacunar stroke but whose etiology can be determined are classified as TOAST-4. Rheumatologic diseases are the

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most important etiologic causes of TOAST-4. Especially young strokes are generally included in this group (3).

The spectrum of rheumatologic diseases is quite broad. Therefore, their neurologic involvement also varies. While some systemic autoimmune diseases affect the peripheral nervous system, others affect the central nervous system more. In particular, systemic lupus erythematosus, rheumatoid arthritis, Takayasu's arteritis, polyarteritis nodosa, systemic vasculitis such as temporal arteritis, and rheumatologic diseases such as psoriatic arthritis and ankylosing spondylitis are known to increase the risk of stroke. Sjögren's syndrome and scleroderma are reported to have no significant adverse effects on stroke (4).

We planned to compare patients who were under rheumatology follow-up or who were diagnosed with rheumatologic disease because of etiologic investigations among patients with a diagnosis of stroke in our clinic with patients with other stroke diagnoses. In conclusion, we aimed to shed light on the differences in the stroke severity, age, and mortality status to help identify patients with rheumatologic diagnosis before stroke development and, if possible, to determine the presence of additional risk factors for stroke development in rheumatologic diagnosis.

Materials and Methods

This study was planned as a retrospective study. Selcuk University Clinical Researches Local Ethics Committee approval was obtained before the study (Approval number: 2020-473). The data of patients who were hospitalized with a diagnosis of stroke in the neurology department of Selcuk University Faculty of Medicine Hospital between 2016 and 2020 were used. Patients over the age of 18 years were included in the study. Patients with subarachnoid hemorrhage, epidural and subdural hematoma, and sinus vein thrombosis were excluded from the study. Patients diagnosed with hemorrhagic stroke, ischemic stroke, transient ischemic attack and hemorrhagic infarction were evaluated. Demographic data such as age, gender, comorbid diseases, stroke types, initial neurologic examination findings, blood on admission, magnetic resonance imaging findings, etiologic evaluations, acute treatment requirements, intensive care unit hospitalization requirements, exitus status, discharge medical treatment, and the number of hospitalization days were recorded for each patient. The comorbid diagnoses of these patients were evaluated, and those who had been diagnosed with rheumatological diseases in the past and those who were diagnosed with rheumatological diseases during the etiological examination were recorded. A comparison with the general stroke group was made.

Statistical analysis

After the data of the patients were entered into the SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) program, the distribution analysis of the data was performed using the Shapiro-Wilk test. Categorical variables are expressed as numbers and percentages, continuous variables are expressed as mean±standard deviation if normally distributed, and median (minimum-maximum) if not normally distributed. In independent groups, independent sample t-test or Mann-Whitney U test was used to compare continuous variables and Pearson's chi-square test was used to compare categorical variables. A p-value of 0.05 was considered statistically significant.

Results

The total number of patients included in the study was 2053. Of these patients, 1697 had an ischemic stroke (82.7%), 190 had a transient ischemic attack (9.3%), 146 had a hemorrhagic stroke (7.1%), and 20 had hemorrhagic infarction (1%). The number of patients with rheumatologic diagnoses was 37. Of these patients, 28 (73.7%) had ischemic stroke, 3 (7.9%) had hemorrhagic stroke, 5 (13.2%) had transient ischemic attack, and 1 (2.6%) had hemorrhagic infarction (see Table 1). The mean age of the entire sample was 66.22±14.33 years (19-98), and in terms of gender, there were 1126 male (54.9%) and 924 female (45.1%) patients. In patients diagnosed with rheumatologic disease, the mean age was 51.62±15.88 years and the gender distribution were 21 (56.7%) females and 16 (43.2%) males. The subdiagnosis, gender ratios, and mean age of the rheumatologic patients are shown in Table 2. According to the table, the mean age of patients with rheumatoid arthritis was similar to that of the general sample. In addition, there was a clear female gender predominance in patients with systemic lupus erythematosus and rheumatoid arthritis. There was no significant gender predominance in the other diagnoses.

When the overall sample was evaluated in terms of intensive care hospitalization, it was observed that 865 (42.2%) patients needed intensive care, whereas 1185 (57.8%) patients were followed up only in the ward. When the mortality rates of the patients were analyzed after follow-up, 297 (14.5%) patients died, whereas 1753 (85.5%) patients were discharged. When the same parameters were evaluated for patients with rheumatologic diagnosis, the number of patients requiring intensive care hospitalization was 13 (34.2%), whereas 24 (64.9%) patients were followed up only in the ward. In the mortality evaluation, 5 (13.5%) patients died, whereas 32 (86.4%) patients were discharged from the ward.

According to the TOAST classification, patients diagnosed with ischemic stroke were classified according to their etiology, and their comparison with the entire population is given in Table 3. According to the table, it is noteworthy that the etiology of patients diagnosed with rheumatologic disease is more intense, especially in TOAST-4.

A comparison of the entire stroke population with stroke patients with rheumatologic disease in terms of demographic data, stroke subtypes, intensive care needs, and exitus status is given in Table 4.

According to the table, the mean age of patients with rheumatologic disease was significantly lower than that of the general population (p<0.001). However, no statistically significant difference was found in terms of other parameters.

Table 1: Comparison of groups in terms of stroke subtypes

	Diagnosed without rheumatological disease	Percent	Diagnosed with rheumatological disease	Percent	Entire sample	Percent
Ischemic Stroke	1669	%82.8	28	%75.7	1697	%82.7
Hemorrhagic Stroke	143	%7.1	3	%8.1	146	%7.1
Transient Ischemic Attack	185	%9.2	5	%13.5	190	%9.3
Hemorrhagic Infarct	19	%0.9	1	%2.7	20	%1
Total	2016	%100	37	%100	2053	%100

Table 2: Demographic characteristics of subtypes of rheumatological disease diagnoses

rheumatological diagnosis	number (n)	percent	the average age	female:male
Rheumatoid arthritis	9	%23.7	67.2	8:1
Behcet 's disease	5	%13.2	57.6	2:3
Systemic lupus erythematosus	5	%13.2	45.4	5:0
Granulomatosis with polyangiitis	3	%7.9	55.3	1:2
Familial mediterranean fever	3	%7.9	42.6	1:2
Takayasu's arteritis	3	%7.9	42	1:2
Central nervous system vasculitis	2	%5.3	44.5	0:2
Sjögren's disease	1	%2.6	41	1:0
Anti-phospholipid antibody syndrome	1	%2.6	22	1:0
Ankylosing spondylitis	1	%2.6	37	0:1
Thromboangiitis obliterans	1	%2.6	30	0:1
Polymyositis	1	%2.6	56	0:1
IgG4 related disease	1	%2.6	43	1:0
Unspecified vasculitis	1	%2.6	52	0:1
Total	37	%100	51.62	21:16

Table 3: Etiological evaluation of groups diagnosed with ischemic stroke using TOAST classification

		Patients diagnosed with rheumatological disease	Percent	Entire sample	Percent
TOAST-1	Large vessel atherosclerosis	7	%25	635	%37.4
TOAST-2	Cardioembolic stroke	3	%10.7	275	%16.2
TOAST-3	Small vessel disease or Lacunar stroke	3	%10.7	377	%22.2
TOAST-4	Stroke due to other specified causes	10	%35.7	43	%2.5
TOAST-5	Cryptogenic stroke	5	%17.9	367	%21.6
total		28		1697	

Table 4: Statistical comparison of stroke groups

		Patients diagnosed without rheumatological disease	Patients diagnosed with rheumatological disease	Entire sample	p-value
Age		66.48±14.12	51.62 ±15.88	66.24±14.27	<0.001
Gender	Female	904 (%44.8)	21 (%56.8)	924(%45.1)	p=0.149
	Male	1112 (%55.2)	16 (%43.2)	1128(%54.9)	
Stroke Subtype	Ischemic Stroke	1669 (%82.8)	28 (%75.7)	1697 (%82.7)	p=0.538
	Hemorrhagic Stroke	143 (%7.1)	3 (%8.1)	146 (%7.1)	
	Transient Ischemic Attack	185 (%9.2)	5 (%13.5)	190 (%9.3)	
	Hemorrhagic Infarct	19 (%0.9)	1 (%2.7)	20 (%1)	
Intensive care admission	Yes	852 (%42.3)	13 (%35.1)	865 (%42.2)	p=0.384
	No	1164 (%57.7)	24 (%64.9)	1185 (%57.8)	
Exitus	Yes	292 (%14.5)	5 (%13.5)	297 (%14.5)	p=0.868
	No	1724 (%85.5)	32 (%86.5)	1753 (%85.5)	

Discusion

As stated in the TOAST classification, rheumatologic diagnoses have a defined place in the etiology of stroke (3). Stroke is a vascular disease. In this respect, diseases that cause deterioration in the vascular wall are closely related to stroke. Vascular involvement

also develops in some rheumatologic diseases. Therefore, it would not be an incorrect suggestion to state that some vasculitis increases the risk of stroke.

Vasculitides are classified according to the size of the vessels involved. Temporal arteritis and Takayasu arteritis, which involve large vessels, are present with a more severe neurological picture. Polyarteritis nodosa affects medium-sized arteries. Granulomatosis with polyangiitis involves small vessels. Clinical findings are different from those of large vessel involvement. Bechet's disease can involve any type of vessel. Therefore, it presents a broad clinical picture (4).

Systemic lupus erythematosus (SLE) is a rheumatologic disease in which central nervous system involvement is common. In previous studies, the incidence of stroke in patients with SLE was reported to be between 5% and 18%. However, recent studies have reported that this rate is approximately % 5.6 (6). SLE diagnosis is an independent risk factor for stroke. Antiphospholipid antibody syndrome plays an important role in the etiology of stroke, particularly in young women (7). Antiphospholipid syndrome is frequently seen in individuals with systemic lupus erythematosus and studies have shown that the risk of stroke is 2-fold higher in patients with systemic lupus erythematosus (8).

Rheumatoid arthritis (RA) occurs at a young age and primarily affects the joints. However, other symptoms also occur in different ways at older ages. Cardiovascular involvement and increased risk of stroke are some of these symptoms. Mortality rates after stroke are also reported to be high in these patients (9). In our study population, the mean age of patients with RA was similar to that of the general stroke population. Increasing age, predominance of female gender, and RA diagnosis can be considered significant risk factors for stroke. Therefore, patients with RA diagnosis and healthcare professionals should be aware of stroke-related conditions.

Stroke development is observed in 10%–20% of patients with Takayasu arteritis. It may lead to serious consequences in terms of prognosis, especially because of its involvement in large arteries (10). Vascular imaging, especially digital subtractional angiography (DSA), is very useful in the diagnosis of Takayasu arteritis. In our sample, thrombectomy was performed in the angiography laboratory for the acute treatment of patients admitted under appropriate conditions. All three of our patients with Takayasu's arteritis had no prior diagnosis of Takayasu's arteritis but were suspected and diagnosed during the acute treatment phase.

The most common symptom of temporal arteritis is headache. However, retinal artery occlusion and vision loss may develop in later stages. Because of the involvement of large arteries, there is an increased risk of stroke with the involvement of the aorta and its branches (11).

Polyarteritis nodosa usually involves the periphery and is a cause of neuropathy. However, it also causes ischemic stroke or intracranial hemorrhage less frequently (12).

Behcet's disease, which is quite common, especially in our country, is a multisystemic disease involving vessels. Central nervous system involvement is mostly seen as parenchymal involvement or sinus venous thrombosis. Recent publications indicate that the risk of stroke in patients with Bechet's disease is 2.27 times higher than that in the normal population (13).

Three patients had granulomatosis with polyangiitis. One of them was diagnosed with hemorrhagic stroke. They had a significant rate of 7.9% among patients with rheumatologic disease diagnosis and stroke. In population-based studies, it has been reported that the risk of stroke increases in granulomatosis with polyangiitis, but not to a statistically significant level (14).

Thromboangiitis obliterans is a disease seen in young men and heavy smokers. The etiology of stroke can be found in the literature as single case reports (15). We also had a patient with Buerger's disease in our series.

The risk factors for ischemic stroke and cardiovascular disease are similar. The risk of cardiovascular and cerebrovascular disease was highest at or soon after the diagnosis of anti-neutrophil cytoplasmic antibody-associated vasculitis and cryoglobulinemic vasculitis. Acetylsalicylic acid (ASA), in particular, reduces the risk of stroke in temporal arteritis and Kawasaki disease. In Behcet's disease, immunosuppressive therapies should be preferred over anticoagulants (16).

Our study had some limitations. In particular, in the class considered cryptogenic stroke, there may be patients diagnosed with rheumatologic diseases that have not yet been diagnosed. As the total number of patients followed up in the rheumatology outpatient clinic and their subdiagnosis were not known, the contribution of these diseases in the development of stroke and risk increases could not be evaluated. Our study is a single-center experience. Regional risk factors may affect stroke development. Therefore, studies conducted in different centers may not yield the same results. In addition, some diseases, such as Bechet's disease, may be observed at different rates in other regions. We do not have sufficient data to make a risk assessment.

Conclusion

Some rheumatologic diseases pose a risk of stroke development. In our study, the mortality rate and intensive care hospitalization rate of patients diagnosed with rheumatologic disease were similar to those of the general stroke population. Although female gender predominance was more prominent in some rheumatologic diseases, overall gender ratios were similar in the entire sample.

In addition, it was determined that patients diagnosed with rheumatologic diseases had strokes at a younger age. As is known, having a stroke is itself a risk factor for recurrent stroke. In addition, in patients who have had a stroke at a young age, another risk develops with increasing age. In this respect, we can say that rheumatologic patients have more than one risk factor for stroke. We believe that patients with rheumatologic diseases, which are known to increase the risk of stroke, should be followed up more closely, awareness of stroke should be increased, additional risk factors should be evaluated in terms of prophylaxis if identified, and a multidisciplinary approach should be taken in the axis of rheumatology-neurology.

Ethical Statement: The study protocol was approved by the Selcuk University Clinical Researches Local Ethics Committee (Approval number: 2020-473). Our study was conducted according to the criteria set in the Declaration of Helsinki.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT

Pityriasis Rosea-like Drug Eruption Due to Isotretinoin

Isotretinoine Bağlı Gelişen Pitriasis Rosea Benzeri İlaç Döküntüsü

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ABSTRACT

Healthcare professionals often encounter the challenge of drug-induced skin eruptions in their daily practice. Typically, dermatologists are tasked with diagnosing these conditions, which can vary from common rashes to specific dermatoses. Our report highlights two patients who experienced a pityriasis rosea-like eruption due to systemic isotretinoin treatment for acne vulgaris

Keywords: Pityriasis rosea, Isotretinoin, Eruption

ÖZ

İlaçla ilişkili deri döküntüleri dermatoloji pratiğinde sık görülmektedir. Bu durumların tanısı diğer uzmanlık alanı çalışanları için zorlayıcı olabildiği için çoğunlukla dermatoloji hekimlerinin alanına girmektedir. Sık görülen makülopapüler ilaç döküntüleri dışında spesifik dermatozların benzeri durumlarda görülebilmektedir. Kliniğimizde akne vulgaris tanısıyla sistemik isotretinoin tedavisi alırken pitriasis rosea benzeri döküntüsü gelişen iki hastayı bildirmek istiyoruz.

Anahtar Kelimeler: Pitriasis Rosea, İsotretinoin, Döküntü

Introduction

Skin eruptions caused by medications are commonly observed in daily medical practice. The diagnosis of such conditions is often based on intuition and guesswork, but in a certain group of patients, a definite conclusion can be made through drug-related tests and evaluations. It is important to note that some drug-induced skin eruptions can resemble common skin diseases, making accurate diagnosis challenging (1).

Pityriasis rosea (P.rosea) is a common, acute-onset disease; have not a clearly known etiology. Many cases of drug-induced P.rosea have been reported. In drug-induced P.rosea cases, failure to recognize and timely discontinue the potentially responsible drug may lead to prolonged course and difficulties in treatment.

We would like to report 2 cases presenting as P.rosea which we thought to be eruption induced by isotretinoin.

Case-1

A 14-year-old female patient admitted to our outpatient clinic with the complaint of pruritic rashes. In her anamnesis, it was learned that the rashes started 5 days ago and increased over time. Dermatologic examination revealed erythematous, collar-like squamous macules and plaques especially on the neck, anterior and posterior aspect of the trunk, flexor aspects of the upper extremities and thighs. (Figure-1a) Oral mucosa and nails were normal. It was determined that the patient had not had any recent infection and had no additional systemic disease. When drug use was questioned, it was found that she had been receiving systemic isotretinoin treatment at a dose of 20 mg/day for 5 months with a diagnosis the acne vulgaris. Laboratory tests revealed normal active inflammation markers and no additional features. The patient was diagnosed as P.rosea-like isotretinoin rash with clinical findings and systemic isotretinoin treatment was discontinued and systemic steroid treatment was started. On the 10th day examination, it was observed that the lesions regressed almost completely (Figure-1b). Verbal consent was granted from patient fort his report.

Case-2

A 20-year-old woman was admitted to our outpatient clinic with complaints of pruritus and rash. In her anamnesis, it was stated that the rashes started 2 days ago. Dermatologic examination revealed the presence of some collar-like squamous plaque lesions

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Table-1. Drugs reported to cause Pytriasis rosea-like rash

Domperidone	Ondansetron	Bismuth	Omeprazole
Imatinib	Nortriptyline	Clozapine	Ergotamine
Ibrutinib	Bupropion	Metronidazole	Acetyl salicylic acid - Codeine
Asenapine	Rituximab	Lithium	Pristinamycin
Isotretinoin	Terbinafine	Benfluorex	Captopril
Atenolol	Lamotrigine	Infliximab	BCG immunotherapy
Vaccines (Covid19, tbc, pneumococcal, hepatitis etc.)			

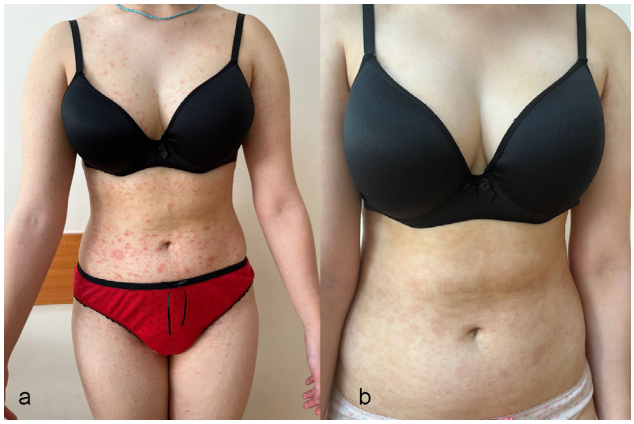

Figure 1:

located on the abdominal wall and pubis. (Figure-2) Oral mucosa and nails were normal. It was reported that she had no recent infection and no additional systemic disease. Laboratory tests were unremarkable. In the medication history, it was found that the patient had been receiving systemic isotretinoin treatment at a dose of 20 mg/day for acne vulgaris for 4 months. Biopsy was taken from the patient before treatment. Histopathologic examination revealed intermittent parakeratosis, orthokeratosis and subacute spongiotic dermatitis. The patient was diagnosed as P.rosea-like isotretinoin rash and systemic isotretinoin treatment was discontinued and systemic steroid treatment was started. The lesions regressed within 1 week. Histopathologic examination was interpreted as nonspecific dermatitis. Verbal consent was granted from patient fort his report.

Systemic isotretinoin treatments was discontinued and not restarted in both patients after eruption resolved.

Discussion

As the skin is a common target for drug reactions, dermatologists have a critical role in recognizing and managing drug reactions. Drug reactions may present with unique clinical pictures or they can also be seen mimicking common skin diseases.

P.rosea is one of the common skin diseases. Its incidence is between 0.5-2% and it is frequently observed in the 15-30 age group (2). It is characterized by erythematous squamous plaques with an exanthematous appearance. The distinctive features are that the squames are in the shape of a collar and the first lesion to appear is in the shape of a medallion (Herald patch). Although the etiology is not known with certainty, viral infections, autoimmunity, psychogenic factors, and drugs are among the causes

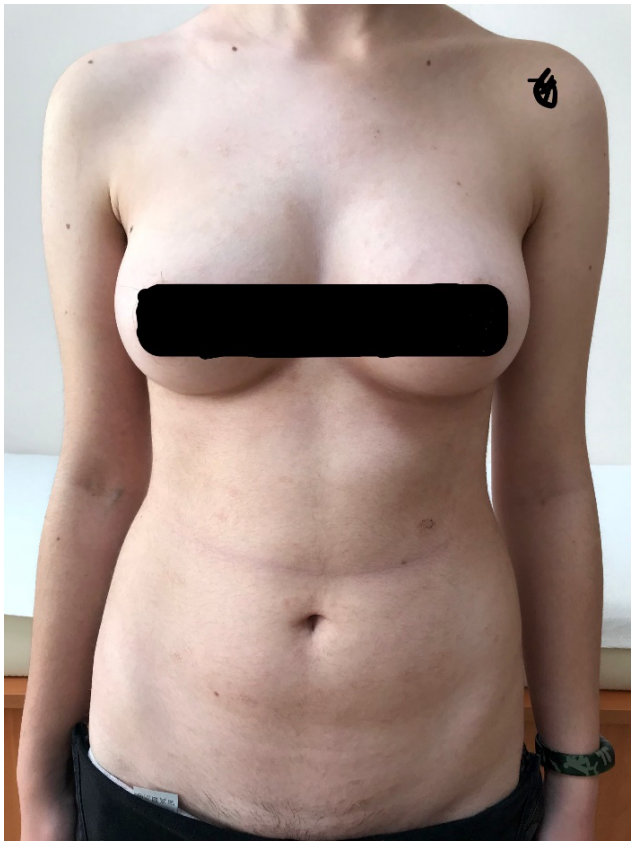

Figure 2:

(3). Endogenous reactivation of human herpes virus 6 and 7 (HHV-6, HHV-7) is one of the factors blamed in the etiology (4). Prodromal symptoms, including headache, malaise, and fever may be observed in some patients. There are many drug-induced P.rosea case reports in the literature. These drugs include atenolol, bismuth, gold salts, clozapine, omeprazole and isotretinoin (Table-1).

There are some clues that can be used to differentiate P.rosea cases thought to develop due to drugs from idiopathic P.rosea;

- Lack of Herald patch

- The color of the lesions is more vivid and prominent

- Itching is severe and does not respond to antihistamines

- Increased eosinophil infiltration in the skin

- Absence of prodromal symptoms such as headache and fatigue

- Lesions regress in a shorter time than classic P.rosea (1,5,6)

Herald patches were absent in two of our cases, the clinical presentation was characterized by multiple plaques with vivid erythematous plaques in the first case and more limited lesions in the second case. Pruritus was the major symptom in both cases. Histopathologic examination was not performed

in the first case because of the typical clinical appearance, whereas histopathologic examination of the second case revealed intermittent parakeratosis, orthokeratosis and subacute spongiotic dermatitis.

Isotretinoin is an agent used in the treatment of moderate to severe acne vulgaris. Although many mucocutaneous and systemic side effects are known, P.rosea-like drug rash has been reported in isolated case reports. Isotretinoin received FDA approval in 1982 and was first reported to cause P.rosea-like rash by Helfman et al. in 1984 (7). The second case report in the literature was made by Gürel et al. in 2018. According to our estimation, our cases will be the third report in the literature.

In our two cases, rash developed while receiving systemic isotretinoin treatment. In the first case, the rash was observed in the fifth month of treatment, while in the second case, the rash appeared in the sixth month of treatment.

The cause and mechanism of P.rosea-like drug eruption is not clearly known. Melnik suggests that the use of isotretinoin induces apoptosis and it can be play a role to develop P.rosea like rash. (8)

The rate of drug reactions with P.rosea-like rash is not clearly known. The fact that it shows differences compared to the classical form and the presence of a drug history are helpful in making the diagnosis. Drago et al. reported that the lesions of 12 patients who were thought to have P.rosea-like drug eruption regressed within 2 weeks after discontinuation of the suspected drugs, which is shorter than 6 weeks, the recovery period of classical P.rosea (9). Similar rapid regression was also observed by Drago et al. in patients with vaccine-associated P.rosea, and the duration of regression of lesions in patients with vaccine-associated P.rosea was observed as 2 weeks (6).

The age range in which classical P.rosea is frequently observed is between 15-30 years while the age range of P.rosea cases thought to develop drug-induced is mostly over 30 years. The increased likelihood of systemic diseases after the third decade and the increase in the rate of drug use are considered to be the reasons for this age difference (6).

Prodromal symptoms such as headache, malaise and fever, which can be observed in patients with classical P.rosea, are not observed in patients with P.rosea thought to develop drug-related. Two of our patients stated that they had no symptoms before the lesion emergence.

In conclusion, dermatologists should be knowledgeable about drug reactions. Controlled prospective studies are needed to understand better and define drug-induced P.rosea.

Conflict of Interest Statement:

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

Author Contributions:

Conception: C.Y., Data Collection: and Processing: C.Y., B.T., Design: : C.Y., B.T., Supervision: C.Y., B.T. F.T.A., G.S.K., Analysis and Interpretation: C.Y., B.T., Literature Review: C.Y., B.T., Writer: C.Y., B.T., Critical Review: C.Y., B.T. F.T.A., G.S.K.

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CASE REPORT

A Case of Visceral Leishmaniasis Characterized by Fever of Unknown Origin and Nodular Lesions in the Spleen

Nedeni Bilinmeyen Ateş ve Dalakta Nodüler Lezyonlar ile Karakterize Bir Visseral Leishmaniasis Olgusu

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ABSTRACT

Introduction: Leishmaniasis is a zoonosis caused by Leishmania spp. parasites through the bite of infected female sandflies, and has three main forms: visceral (VL), cutaneous (CL) and mucocutaneous (MCL). VL is endemic in many countries around the world. It is on the World Health Organization's (WHO) list of neglected diseases and is difficult to diagnose due to its non-specific clinical manifestations. VL is characterized by fever, hepatosplenomegaly and bone marrow suppression. The diagnosis is made by the presence of amastigotes in tissue or blood samples or serological and DNA-based techniques.
Case: Our patient was a 30-year-old male who did not have any immunodeficiency. He was characterized by persistent fever, pancytopenia, hepatosplenomegaly and multiple millimetric hypoechoic solid nodules in the spleen. The diagnosis of VL was confirmed using all three parasitological, serological and molecular methods. Cure was achieved by treatment with liposomal amphotericin B (L-AmB).
Conclusion: VL should be considered in the differential diagnosis of patients with fever of unknown cause, pancytopenia and hepatosplenomegaly. The presence of solid nodular lesions in the spleen may also shed light in favour of VL.

Keywords: Fever of unknown cause, hepatosplenomegaly, pancytopenia, splenic nodule, visceral leishmaniasis

ÖZ

Giriş: Leishmaniasis, enfekte dişi tatarcık sineklerinin ısırması sonucu Leishmania spp. parazitlerinin neden olduğu bir zoonoz olup visseral (VL), kutanöz (KL) ve mukokutanöz (MKL) olmak üzere üç ana formu vardır. VL dünyada birçok ülkede endemik olarak bulunur. Dünya Sağlık Örgütü'nün (DSÖ) dikkat çektiği ihmal edilen hastalıklar listesinde olup, spesifik olmayan klinik bulguları nedeniyle tanı konulması zor bir hastalıktır. VL ateş, hepatosplenomegali, kemik iliği süpresyonu ile seyreder. Tanı doku ya da kan örneklerinde amastigotların görülmesi veya serolojik ve DNA esaslı tetkikler ile konur.
Olgu: 30 yaşında immün yetmezlik öyküsü olmayan erkek hastada persistan ateş, pansitopeni, hepatosplenomegali ve aynı zamanda dalakta çok sayıda milimetrik hipoekoik solid nodüller mevcuttu. Parazitolojik, serolojik ve moleküler yöntemlerin üçü de kullanılarak VL tanısı kesinleştirildi. Lipozomal amfoterisin B (L-AmB) ile tedavi edilerek kür sağlandı.
Sonuç: Nedeni bilinmeyen ateş, pansitopeni ve hepatosplenomegali olan hastalarda ayırıcı tanıda VL düşünülmelidir. Dalakta solid nodüler lezyonların varlığı da VL tanısına ışık tutabilir.

Anahtar Kelimeler: Dalakta nodül, hepatosplenomegali, nedeni bilinmeyen ateş, pansitopeni, visseral leishmaniasis

Introduction

Leishmaniasis is a parasitic zoonotic disease transmitted by the bite of infected female sandfly (Phlebotomus), one of the tropical diseases considered important by the World Health Organization (WHO). Dogs, foxes, jackals and other Canidae are reservoirs of the parasite in nature. There are 3 main forms: visceral (kala-azar) (VL), cutaneous (CL) and mucocutaneous (MKL). CL is the most common form. VL is the most serious form and is fatal if not diagnosed and treated. Leishmaniasis is endemic in 99 countries, including Türkiye and other countries in the Mediterranean region, as well as underdeveloped countries in America, East and North Africa, and West and Southeast Asia. Increased travelling, migration movements and climate change as a result of global warming increase the prevalence of leishmaniasis worldwide. According to WHO data, it is estimated that between 50.000 and 90.000 new cases of visceral leishmaniasis develop annually in the world, but it is thought that less than half of them is reported. VL is characterized by fever attacks, weight loss, hepatomegaly, splenomegaly and pancytopenia. Definitive diagnosis is made by demonstration of amastigotes in tissue or blood samples. However, various serological tests based on the detection of specific anti-Leishmania antibodies and DNA-based molecular techniques are also used (1-4). In this case report, we present a patient who was initially suspected to have haematological malignancy due to persistent fever, bone marrow suppression and the presence of multiple nodular solid lesions in the spleen, but was diagnosed with VL in the clinical progress.

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Case

A 30-year-old male patient living in a rural area of Konya presented to our outpatient clinic with complaints of fever, weakness and weight loss for ten days during the summer months. In his anamnesis, he had no history of travelling anywhere other than the district where he lived. He had a history of tick bite one week ago. There was no known underlying disease. On physical examination, fever was 39°C, pulse 94/minute, BP 110/70 mmHg, and hepatosplenomegaly was determined. Laboratory examination revealed haemoglobin 13.9 g/dl, leukocyte 3830/mm3, platelet 95 thousand/mm3, erythrocyte sedimentation rate (ESR) 27 mm/h, CRP 120.5 mg/L, AST 62 U/L, ALT 57 U/L, LDH 597 U/L, CK 61 U/L, INR 1.35 and ferritin 4599 µg/L. Brucella and Salmonella agglutination test and Crimean-Congo haemorrhagic fever ELISA test, Hbs Ag, anti HCV, anti-HIV, CMV IgM, toxoplasma IgM, EBV VCA IgM, HSV IgM and VDRL tests ordered for differential diagnosis were negative. Thyroid function tests were normal. His chest X-ray was normal with no infiltrations. No pathological findings were found on echocardiography. Respiratory tract microarray polymerase chain reaction (PCR), including COVID, was performed and nothing was detected. Spleen long axis was 170 millimeters (mm) on abdominal ultrasonography.

During the follow-up of the patient who was followed up due to fever of unknown origin, bone marrow suppression increased and AST, ALT, ALP, GGT and CK levels continued to increase among biochemical parameters. Persistent fever (>38 °C) continued. No growth was detected in the blood culture samples taken. Abdominal computed tomography (CT) showed liver size of 180 mm in vertical dimension, spleen size of 190 mm, and hypoechoic solid nodular foci with heterogeneous parenchymal appearance. Abdominal magnetic resonance imaging (MRI) showed multiple millimetric nodular lesions in the splenic parenchyma less than 10 mm in size, which were less contrasted with the parenchyma in arterial phase imaging and had equal signal with the parenchyma in other phases (Figure 1). Blood examination was performed for malaria and it was not detected. No atypical cell was detected in peripheral blood smear. Considering that the etiology of the lesions in the spleen and fever had not yet been elucidated, it was decided to perform a bone marrow biopsy to exclude or demonstrate hematological malignancy. No growth was detected in the blood culture sent from the bone marrow aspirate. On examination of the bone marrow aspirate, findings suggestive of haemophagocytic syndrome were found. In the follow-up, Leishmania spp. IgG and PCR results were found positive by dipstick in serum and blood samples sent to the National Microbiology Reference Laboratory of Public Health of Türkiye, and peripheral blood smear and bone marrow preparations were examined by an expert parasitologist and Leishmania spp. amastigote forms were detected in the microscopic examination (10x100) of Giemsa-stained smears (Figure 2). Parenteral 3mg/kg/day liposomal amphotericin B (L-AmB) was started with the diagnosis of VL. After 72 hours of treatment, the patient's fever decreased and other complaints regressed. On laboratory examination, bone marrow suppression findings and biochemical parameters regressed. Control peripheral blood smear examination on the fifth day showed rare amastigotes. The patient was discharged after five days of L-AmB treatment. L-AmB dose was repeated on the 14th and 21st days of treatment initiation and terminated. No Leishmania amastigotes were observed in the peripheral blood smears performed at the end of the treatment. Abdominal ultrasonography showed regression of hepatosplenomegaly. No pathological findings were found in the third month outpatient clinic control and the patient was considered cured.

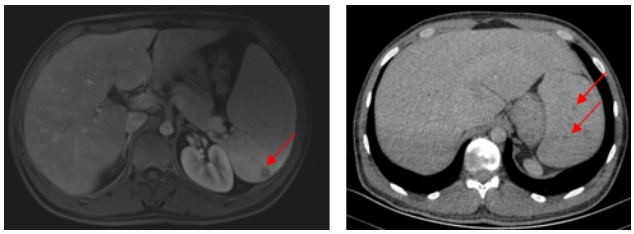

Figure 1. Nodular lesions in the spleen on MRI (1a) and CT (1b) imaging

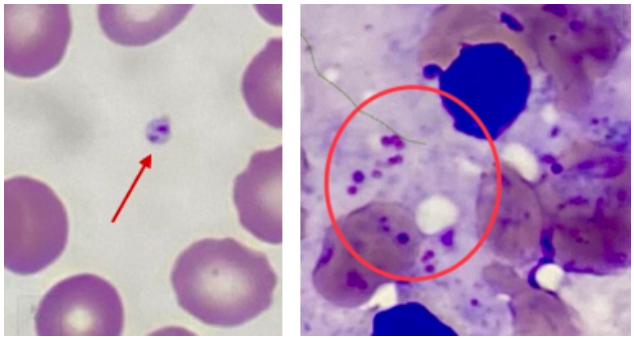

Figure 2. Amastigotes in peripheral blood smear (2a) and bone marrow aspirate (2b)

Discussion

Leishmaniasis is one of the zoonotic diseases which is endemic in the Mediterranean region including Türkiye and is caused by more than 20 species. However, VL is observed as sporadic cases in Türkiye, mainly in the Aegean and Mediterranean regions (5-8). Therefore, it may not be considered in the differential diagnosis outside these regions. Since our patient lived in Konya, a Central Anatolian city and had no history of travelling outside the province, VL was not primarily considered. When the literature was analyzed, the presence of vector flies in this region was found (9). Considering the presence of vector flies and reservoir dogs, our patient may have been infected.

Visceral leishmaniasis is characterized by fever, hepatosplenomegaly and pancytopenia. Due to its non-specific clinical findings, the diagnosis is delayed and may cause morbidity and mortality. It may also be confused with haematological malignancies. The gold standard in diagnosis is the observation of amastigotes in the infected material on microscopic examination

in preparations stained with giemsa. Serological and molecular methods are also used in diagnosis (3, 6). In the literature, although similar findings including fever, hepatosplenomegaly, anaemia, leucopenia and weight loss are common, few cases have nodules in the spleen or liver on abdominal imaging (10-14). Our patient had similar clinical and laboratory findings. In addition, multiple solid nodules were found in the spleen on abdominal imaging. The presence of hypoechoic nodules in the spleen is generally associated with lymphoma, splenic infarction, metastatic disease, septic embolism and granulomatous diseases (15). However, we saw that there may be a similar image in VL. We think that it should be included in the possible differential diagnosis of these focal lesions in the spleen and liver.

While malignancy was considered in the foreground in the patient, the diagnosis was made when Leishmania amastigotes were observed in the bone marrow aspirate sample examined upon positive Leishmania IgG test in the serum blood sample. The presence of Leishmania was also demonstrated by PCR method.

Currently treatment of VL, antimony compounds and amphotericin B compounds are used. However, L-AmB has been preferred recently because of its less side effects and toxicity. In a non-immunosuppressed patient, parenteral L-AmB 3mg/kg/day on days 1-5 and days 14 and 21, totalling 21mg/kg (3, 4). L-AmB was also used in our patient and a dramatic improvement was observed in his complaints after 72 hours.

In conclusion, VL should be considered in the etiology of fever of unknown origin in non-endemic regions and it should be kept in mind that the disease may be confused with haematological malignancies because of pancytopenia, hepatosplenomegaly and solid nodule findings in the spleen. In addition, considering the presence of vector flies in our region and the fact that dogs, which are frequently found in our living areas, are the reservoir host of the parasite, it should be taken into consideration by the authorities that sporadic cases of Leishmaniasis in stray, uncontrolled, stray dogs may cause an important public health problem for our region.

Patient Consent: A consent form was obtained from the patient included in our study.

Conflict of Interest: The authors declare no conflict of interest regarding this article.

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