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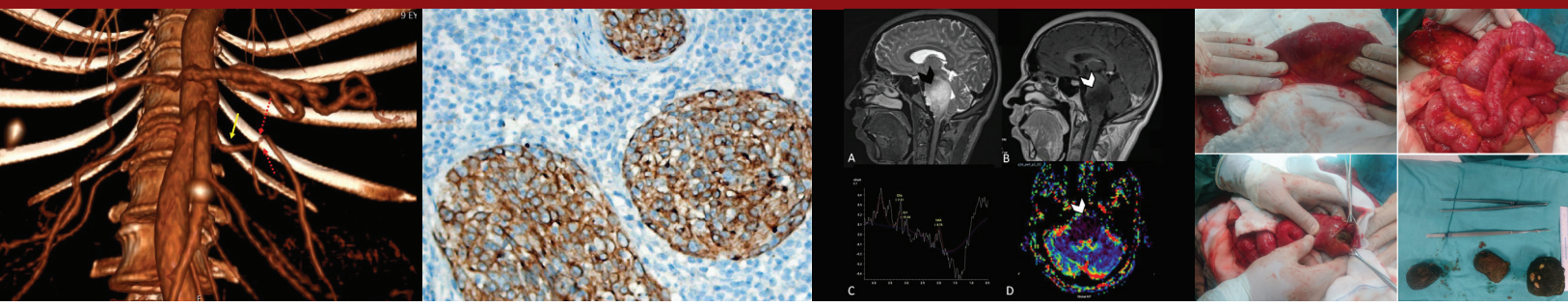

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Aims and Scope

Cyprus Journal of Medical Sciences (Cyprus J Med Sci) is the scientific, peer reviewed, open access international publication organ of Cyprus Turkish Medical Association. The journal is published three times a year, in April, August, and December. The journal's publication language is English.

The aim of the journal is to publish original research papers of the highest scientific and clinical value in all medical fields. Cyprus Journal of Medical Sciences also publishes reviews, rare case report and letters to the editors.

The target audience of the journal includes healthcare professionals physicians, and researchers who are interested or working in in all fields of medicine.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Instruction to Authors

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All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

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- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number), and email address of the corresponding author,
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Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Background/Aims, Material and Methods, Results and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of five keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. Acceptance of original papers will be based upon the originality and importance of the investigation. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. An original article can be signed by maximum 6 authors unless it is a multi-center study or that it required extensive labour. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion with an unstructured abstract. Please check Table 1 for the limitations for Case Reports.

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All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (includ-

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Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIEID/cid.htm.

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Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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Editorial

DOI: 10.5152/cjms.2019.181219

Hello everyone,

I would like to send my best wishes to you all on the behalf of the Cyprus Journal of Medical Sciences Editorial Board. I am very happy to let you know that our journal, following EBSCO and ESCI, is now being indexed in "TUBITAK Ulakbim TR Index." For this, we thank the authorities of the TUBITAK Ulakbim TR Index. Certainly, our next main objective will be to be indexed in SCIE and PubMed.

Another thing that I wish to share is that, from the coming year, our journal will be published four times a year instead of three. We are planning to publish issues in March, June, September, and December. We decided to increase the number of issues because of increased volume of manuscripts sent to our journal and demand for early publication of the articles. Always, our goal is to lead and offer ways to authors for conveying their research. By doing so, all practitioners of medicine as well as patients will benefit-which is our main goal.

We are aware of the fact that we are only a small pinpoint of the enormous topics and fields of medicine, but we want to be part of it and aspire to add something beneficial, no matter how small, to it. In this regard, we must aim to work hard for achieving this purpose.

As always, we are very grateful to our authors and reviewers for their great efforts. We wish to thank to our Publishing House as well for their great assistance and cooperation. Finally, we wish everyone a healthy life and a world with peace and nourishing environment.

My Best regards!

Sonuç Büyük
Editor-in-Chief

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Original Article

DOI: 10.5152/cjms.2019.1023

Reliability and Validity of the Turkish Version of the Revised American Pain Society Patient Outcome Questionnaire in Postoperative Patients

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BACKGROUND/AIMS
The aim of the present study was to evaluate the psychometric properties of the Turkish version of the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R) in postoperative patients.

MATERIAL and METHODS
A descriptive, cross-sectional psychometric study design was used to examine the psychometrics of the Turkish APS-POQ-R among a convenience sample of 218 adult postoperative patients treated by five surgical departments in two hospitals. The 23-item English version of the questionnaire was translated into Turkish according to international guidelines. For the questionnaire, construct validity was analyzed with confirmatory factor analyses and known group validity. Cronbach's alpha was used to examine the questionnaire internal consistency reliability.

RESULTS
The Cronbach's alpha of the questionnaire was .91. Cronbach's alpha coefficients for the subscales were pain severity and sleep interference .87, activity interference .92, affective .95, adverse effects .91, and perception of pain care .50.

CONCLUSION
The Turkish APS-POQ-R was found to have confirmatory factor structure and internal validity and construct reliability similar to the original instrument. The questionnaire appears to be useful to evaluate the quality of pain management in postoperative patients and can be used to guide the implementation of nursing interventions. Further investigation is warranted on the perceptions of care subscale.

Keywords: Patient outcomes, postoperative pain, psychometrics, reliability, revised American pain society patient outcome questionnaire

INTRODUCTION

Acute postoperative pain is a common clinical condition requiring an evidence-based, planned, and multimodal approach (1). Despite the increase in knowledge on the physiology and control of pain, most of the patients do not receive sufficient analgesia or pain control during the surgical period (2).

Data collected by the World Health Organization from 194 countries reveal that approximately 312.9 million major surgical operation occurred in 2012 (3). In the case of Turkey, the annual number of surgical operation is >8.6 million (4). According to the literature, the percentage of patients who suffer from severe pain during the first postoperative day ranges between 20% and 80% worldwide (5, 6) and between 60% and 77% in Turkey (7). Inadequately treated postoperative pain delays recovery and discharge, which in turn decreases patient satisfaction (2).

Whenever possible, postoperative pain should be prevented and controlled. The aim of acute pain management is to prevent postoperative complications, speed up the recovery period, minimize the side effects of analgesics, and prevent

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acute pain from becoming chronic (1, 8). Effective pain management is a central concern of nursing. Inadequate pain management decreases patient satisfaction and may prolong the length of the recovery period and the risk of re-hospitalization (9-11).

Pain management is an important indicator of healthcare quality. Quality pain management is a multidimensional issue that starts with the proper evaluation of pain of the patients and their response to the treatment. Monitoring and evaluation of pain management quality by using the appropriate measurement tools are essential for the improvement of patient outcomes and pain management quality (10, 12).

Gordon et al. (12) identified measurable patient reported outcome domains to evaluate acute pain management quality. These include pain severity and relief; impact of pain on activity, sleep, and negative emotions; side effects of treatment and perceptions of the patients, such as helpfulness of the information received about pain treatment; ability to participate in pain treatment decisions; and satisfaction with the results of the treatment. To develop a standard measurement tool for quality improvement purposes that includes these dimensions, the researchers revised the American Pain Society Patient Outcome Questionnaire (APS-POQ) developed by the American Pain Society in 1991 (American Pain Society Quality of Care Committee, 1995). In the revised questionnaires, APS-POQ-R has been used to evaluate the impact of acute postoperative and medical condition-related pain in hospitalized adults and has been translated into 12 different languages (12-16), for example, Chinese, Australian, and Icelandic versions (13, 15, 16).

Although there are various questionnaires in Turkish used to identify pain sources and severity (17-19), there is no measurement tool to evaluate the quality of pain management using patient reported outcomes together with pain treatments. Such a tool may aid the health professionals to evaluate the postoperative pain management quality, effects of pain on patient outcome, patients' activity and mood, and side effects of pain and pain management. This methodological study has been conducted to evaluate the reliability and validity of the Turkish version of the APS-POQ-R.

Research Questions

1. What is the reliability coefficient of the Turkish version of the APS-POQ-R?
2. Isw the confirmatory factor analysis in harmony with the preliminary factor structure?

MATERIAL and METHODS

This methodological study was conducted at the general surgery and orthopedics, urology, gynecology, and neurosurgery wards of two state hospitals in the Turkish Republic of Northern Cyprus. The study included participants aged >18 years, who underwent minor and major surgical operations, and who stayed at the hospital for at least 24 h.

Studies on scale development, reliability, and validity suggest that the sample size should be at least 200 and 10 times the number of items (20). Based on these criteria, a total of 230 voluntary participants were included to our research. However, owing to the shortcomings in the data collection form of 12 patients, the study was conducted with the participation of 218 voluntary patients.

Data were collected between February 26, 2017 and June 22, 2017. Gordon et al. (12) collected data from patients who received treatment for at least 24 h in a hospital 72 h after the surgical operation. Patients answered a questionnaire on postoperative day 3. Patients who met the inclusion criteria were informed about the aims of the research. Written and verbal consents were obtained from the voluntary participants.

The researchers read the questions to the participants and recorded their responses. Descriptive data on age, gender, clinic, type and location of surgery, type of analgesics, and route of analgesics administration were obtained from the patient files and recorded to the Descriptive Characteristics Form. Data on pain management quality and patient outcome were collected by using the APS-POQ-R.

The APS-POQ-R is composed of 23 items that aim to measure the five dimensions of the pain management quality. Five subscales, which consisted of a total of 18 items, include pain severity and sleep interference (five items), activity interference (two items), affective (four items), adverse effects (four items), and perceptions of care (three items) subscales. Overall, the Cronbach's alpha of the original questionnaire was .86. Additional items in the questionnaire, including information about pain treatment options, the use of non-medication methods, and how often a doctor or nurse encouraged the use of non-medication methods, were evaluated from the subscales.

The responses to the two items on the estimate of percentage of time in severe pain and the pain relief in the first 24 h were measured according to their percentages that ranged between 0% and 100%. The responses to the remaining 16 items of the five subscales were measured by the 0–10 numeric rating scale, which was treated as a continuous scale. Additional items on the use of non-medication methods and receiving information about pain treatment options involved dichotomous yes/no responses. A "yes" response was followed by a request for a more specific response.

The APS-POQ-R was translated and retranslated according to international guidelines (21). It was first translated into Turkish by two experts on the English and Turkish languages. Translation validity of the APS-POQ-R was evaluated by using a retranslation technique. The APS-POQ-R was translated back to English by two experts of the English language who did not see the original APS-POQ-R. Items in the retranslated APS-POQ-R were compared with those in the original scale, and expert opinion was used for evaluating translation validity. To maintain content validity, the scale was evaluated in line with the suggestions of nine clinicians and academicians from the clinics and departments of surgical nursing, basics of nursing, psychiatric nursing, anesthesiology, psychology, and internal medicine. Based on the suggestions, changes were made in three questions. For the "how much pain interfered or prevented you from" question, the expressions were changed from "did not intervene" and "completely intervened" into "did not prevent" and "completely prevented." In the questions "In the first 24 hours, how much pain relief have you received? Please circle the one percentage that

best shows how much relief you have received from all of your *pain treatments* combined" and "Did you use any non-medicine methods to relieve your pain?," the expressions "analgesic" and "ice bag" were replaced with "pain treatment methods" and "cold application," respectively. The APS-POQ-R was modified based on expert opinion, and the questionnaire was finalized.

To evaluate expert opinion, Content Validity Index (CVI) was used (22). While assessing expert opinion, CVI was used, which was evaluated by calculating Item-Content Validity Index (I-CVI) and Scale-Content Validity Index (S-CVI). The I-CVI for each item and the S-CVI for the whole questionnaire were calculated. The I-CVI and S-CVI scores on nine expert opinions were .82 and .84, respectively. I-CVI and S-CVI are suggested to be higher at .80 and .78, respectively (22). The I-CVI and S-CVI scores for this research were .82 and .84, respectively. This finding suggests that there is a consensus among the experts, and that the APS-POQ-R has a clear and intelligible content. Following the evaluation of expert opinion, the suggestions of an expert in the Turkish language were taken to adapt the scale into Turkish.

After maintaining translation and content validity, the APS-POQ-R was administered on 50 voluntary participants to evaluate the extent to which the questions were clear and intelligible. Additionally, an evaluation form was prepared to receive feedback from the participants. The evaluation form consisted of statements, such as "explanations in the APS-POQ-R were clear," "it was easy to follow the APS-POQ-R," "questions in the APS-POQ-R were clear," and "questions in the APS-POQ-R were boring." The participants were asked to express their opinions on these statements by using a five-point Likert scale with categories that ranged from "strongly agree" to "strongly disagree." The analysis of the responses of the participants of the pilot study reveals that 99% of the participants found the Turkish version of the APS-POQ-R as clear and intelligible. Participants in the pilot study were excluded in the final sample.

Statistical Analysis

Data obtained were evaluated by using Statistical Package for the Social Sciences version 18.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics were used to evaluate sample characteristics and pain management results. While evaluating the psychometric characteristics of the Turkish version of the APS-POQ-R, confirmatory factor analysis and known group validity for validity analysis and Cronbach's alpha coefficient and item–total correlation for reliability analysis were used.

The study was approved by the Scientific Research and Publication Ethics Committee of the Eastern Mediterranean University (ET00-2016-0156), Ministry of Health (YTK.0.00-1/2013-16/7303). Written consent was obtained from the participant patients by using an "Informed Voluntary Consent" form. Written permission was also obtained from D.B. Gordon to translate the original APS-POQ-R into Turkish.

RESULTS

The average age of the participants in the sample of this research was 39.7±15.00 years. In the present study, 70.6% of the participants were female, and 39.0% received treatment at the gynecology clinic. Approximately 52.8% of the participants underwent minor surgical operation, 93.1% received non-steroidal anti-inflammatory drug (non-opioid), 80.0% were administered analgesics by intramuscular route, and 51.4% underwent prior operation (Table 1).

Construct validity of the Turkish version of the APS-POQ-R was analyzed, and the results of confirmatory factor analysis in the modified model were shown to be acceptable. Chi-square/p value was 328.41/0.000 ($p<.05$), chi-square degree of freedom was 2.67, root mean square error of approximation (RMSEA)/p value was .088 ($p<.05$), and standardized root mean square residual (SRMR) value was .12. Adjusted goodness of fit index (AGFI), comparative fit index (CFI), non-normed fit index (NNFI), and goodness of fit index (GFI) that were created to test the resultant model were .80, .96, .95, and .86, respectively, further supporting that the model was acceptable. When the factor loads of the items of the APS-POQ-R were analyzed, we found that the item "allowed to participate in decisions about pain treatment" had a factor load of .17, whereas the factor loads of the remaining 17 items ranged between .56 and .96 (Figure 1).

Construct validity of the APS-POQ-R was analyzed by using known group validity. Gender, age, prior surgical experience,

TABLE 1. Characteristics of the surgical patients (N=218)

Variables	N	%
Age		
≤60 years	193	88.5
>60 years	25	11.5
Gender		
Female	154	70.6
Male	64	29.4
Location of surgery		
Abdomen/anorectal	144	66.1
Orthopedics	58	26.6
Head/neck/lumbar	16	7.3
Type of surgery		
Minor surgery	115	52.8
Major surgery	103	47.2
Type of analgesic		
Opioid	7	3.2
NSAID	203	93.1
Opioid+NSAID	8	3.7
Route of administration of analgesics		
IV	43	13.0
IM	178	80.0
Oral	16	7.0
History of surgery		
Yes	112	51.4
No	106	48.6
Total	218	100.0

NSAID: non-steroidal anti-inflammatory drug; IV: intravenous; IM: intramuscula

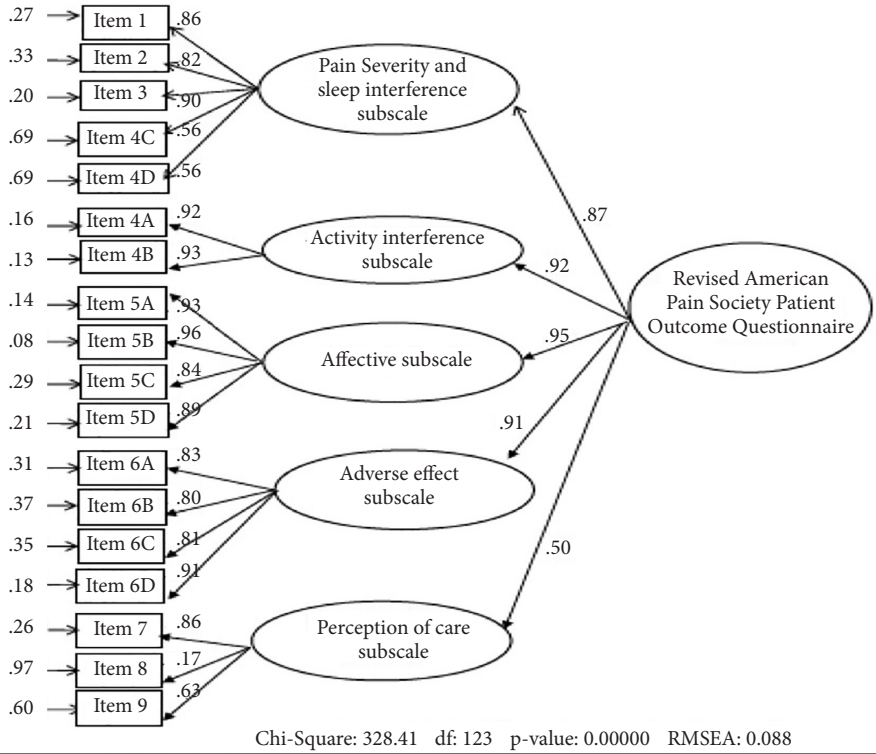

FIGURE I. Confirmatory factor analysis of APS-POQ-R: path coefficients and error variances (N=218)

TABLE 2. Mean differences of APS-POQ-R subscales in known group patients (N=218)

		APS-POQ-R Subscales				
Variables	**n**	**Pain severity and sleep interference M±SD**	**Interference with activity M±SD**	**Affective M±SD**	**Adverse effects M±SD**	**Perceptions of care M±SD**
Age						
≤ 60	193	6.86±1.99	7.14±2.23	5.67±3.14	4.47±3.11	5.33±1.96
> 60	25	6.88±1.97	6.80±2.50	5.19±3.50	4.41±3.29	6.09±2.06
Z		.113	.419	.552	.078	1.852
p*		.910	.676	.581	.938	.064
Sex						
Female	154	7.08±1.92	7.31±2.01	6.00±3.05	4.88±3.14	5.60±1.98
Male	64	6.32±2.03	6.59±2.73	4.71±3.31	3.46±2.88	4.97±1.93
t		2.633	1.902	2.774	3.225	2.152
p*		.009	.060	.006	.002	.033
Surgery type						
Minor	115	6.48±1.99	6.78±2.44	5.20±3.09	4.42±3.19	5.11±1.96
Major	103	7.28±1.89	7.46±2.00	6.08±3.23	4.50±3.07	5.77±1.96
t		3.031	2.247	2.052	.206	2.479
p*		.003	.026	.041	.837	.014
History of surgery						
Yes	112	6.87±1.96	7.22±1.98	5.58±3.24	4.76±3.13	5.38±2.08
No	106	6.85±2.01	6.98±2.53	5.66±3.12	4.14±3.10	5.46±1.89
T		.104	.790	.185	1.461	.267
p*		.917	.430	.853	.146	.790

M±SD: mean ± standard deviation
*p<.05

type of surgical operation (minor–major), and average scores of the subscales of the APS-POQ-R were evaluated (Table 2). The analysis of the relationship between gender and the average scores of the subscales reveals a significantly meaningful relationship between being female and the subscales of pain severity and sleep interference, affective, and adverse effects (p<.01). On the other hand, the average score obtained by the female participants from the perceptions of care subscale was meaningfully higher than that by all participants (p<.05). Although the average scores obtained by the female participants from the activity interference subscale are higher than those by the male participants, the relationship was not statistically meaningful (p>.05).

The analysis of the relationship between age and prior surgical experience of the participants and the average scores of the subscales of the APS-POQ-R reveals no meaningful relationship between these variables (p>.05). Compared with those who had minor surgical operation, participants who underwent major surgical operation had significantly meaningful scores from pain severity and sleep interference subscale (p<.01) and meaningful scores from activity interference, affective, and perceptions of care subscales (p<.05). On the other hand, the relationship between the type of surgery and adverse effects subscale was not statistically meaningful (p>.05).

The internal consistency reliability of the APS-POQ-R is shown in Table 3. Cronbach's alpha coefficient of the 18 items of the APS-POQ-R was .91. Cronbach's alpha coefficients for the subscales of the APS-POQ-R were .87 for pain severity and sleep interference, .92 for activity interference, .95 for affective, .91 for adverse effects, and .50 for perception of pain care. Cronbach's alpha if the item was deleted for the APS-POQ-R was between 90 and 92, whereas item–total correlation was between .27 and .83 and was positive and statistically highly meaningful (p<.01) (Table 3).

Descriptive statistics of additional items of the APS-POQ-R are shown in Table 4. Accordingly, 75.7% of the patients stated that they did not receive information about pain treatment options. For participants who expressed that they received information about pain treatment options, the average score for the additional item on the helpfulness of the information was 6.91±2.02. In addition, 56.4% of the participants stated that they did not

TABLE 3. Item to total correlations and Cronbach's alpha (N=218)

Item's No	Subscales and items	Cronbach's Alpha of subscale	Corrected item-total correlation		Cronbach's Alpha if item deleted
			r≠	p*	
	Total Scale	.91			
	Pain severity and sleep interference subscale	.87			
1	Least pain		.56	<.001	.91
2	Worst pain		.38	<.001	.91
3	Percentage of time in severe pain		.56	<.001	.91
4C	Pain interfered falling asleep		.75	<.001	.90
4D	Pain interfered staying asleep		.75	<.001	.90
	Activity interference	.92			
4A	Pain interfered activities in bed		.51	<.001	.91
4B	Pain interfered activities out of bed		.58	<.001	.91
	Affective	.95			
5A	Pain caused to feel anxious		.79	<.001	.90
5B	Pain caused to feel depressed		.83	<.001	.90
5C	Pain caused to feel frighten		.75	<.001	.90
5D	Pain caused to feel helpless		.77	<.001	.90
	Adverse effect	.91			
6A	Nausea		.70	<.001	.90
6B	Drowsiness		.72	<.001	.90
6C	Itching		.73	<.001	.90
6D	Dizziness		.76	<.001	.90
	Perception of care	.50			
7	Pain relief		.49	<.001	.91
8	Participate in decisions about pain treatment		.27	<.001	.92
9	Satisfied with the results of pain treatment		.35	<.001	.91

≠r: Pearson correlations
*p<.001

TABLE 4. APS-POQ-R descriptive statistics of other items (N=218)

Items	n	%
Did you receive information about pain treatment options?		
Yes	53	24.3
No	165	75.7
	Min-Max	M±SD
How helpful information was if received? (n=53) [a]	3-10	6.91±2.02
	n	%
Did you use any nonmedication methods?		
Yes	95	43.6
No	123	56.4
Used non pharmacological methods (n: 95)[b]		
Deep breathing	39	41.1
Walking	22	10.2
Praying	16	7.8
Cold pack	13	7.2
Listen to music	9	8.5
Heat	8	8.4
Distraction (Watching Tv, reading etc.)	19	20.3
Did a doctor or nurse encourage nonmedication methods?		
Never	191	87.6
Sometimes	18	8.3
Often	9	4.1
Total	218	100

Max: maximum score; Min: minimum score; M±SD: mean ± standard deviation

[a]The averages are calculated on 53 people (n=53)

[b]More than one option is marked. Percentages are calculated over 95 people (n=95)

use non-medication methods. For participants who expressed that they used non-medication methods (n=95), 41.1% stated that they used deep breath method, and 87.6% said that the doctor or nurses did not encourage non-medication methods.

DISCUSSION

The present study, which originated from the need for the development of a measurement tool in Turkish to evaluate pain management quality and include patient reported outcomes, adapted the APS-POQ-R into Turkish (12). The items of the APS-POQ-R were first translated into Turkish, and the translation and content validity of the Turkish version were evaluated. Next, the psychometric characteristics, internal consistency, item reliability, and construct validity of the APS-POQ-R were evaluated.

Studies that have been conducted to adapt the existing questionnaires into different cultures and languages suggest the use of confirmatory factor analysis to analyze construct validity (23, 24). In line with the suggestions in the literature, confirmatory factor analysis was conducted to evaluate the construct validity of the APS-POQ-R. Factor load of the item "allowed to participate in decisions about pain treatment" was .17, whereas the factor loads of the remaining 17 items ranged between .56 and .96 (Figure 1). Factor loads of the items in the subscales were suggested to be equal to the factor loads and at least .30 (23). With the exception of the eighth item, all of the items in the Turkish version of the APS-POQ-R had a factor load >.30. Low factor load for the eighth item on allowing the patients to participate in decisions about pain treatment indicates that the participation of the patients and their relatives in treatment procedures is not common in the Turkish hospitals included in the present study. An indication that the culture of healthcare in these hospitals needs to improve should include the patient in treatment decisions.

While evaluating confirmative factor analysis, goodness of fit analysis is expected to be at normal levels. For a reasonable model, chi-square goodness of fit test should not be meaningful. This value may be achieved when the sample size is greater. Owing to this reason, in place of chi-square goodness of fit, chi-square value is divided by degree of freedom. The model is compatible if the value obtained is <2, whereas the model is considered to be at acceptable compatibility levels if the value is <5 (23). This value in the confirmatory factor analysis of the Turkish version of the APS-POQ-R was 2.67, indicating an acceptable compatibility level.

Another goodness of fit test that is frequently used is the RMSEA. This test suggests that an RMSEA score ≤.08 and a p value >.05 indicate goodness of fit (23, 24), and that an RMSEA score ≤.10 shows low levels of goodness of fit (23). The present study, which calculated the RMSEA value as meaningful and .088 (p<.001), found that the compatibility for the factorial structure was weak but at acceptable limits. A value of SRMR <.10 and the values of CFI and NNFI ≥0.90 indicate goodness of fit (23). A value >.95 indicates goodness of fit, whereas a value >.90 indicates acceptable goodness of fit (23, 24). The present study found that the CFI and NNFI values were .96 and .95, respectively, indicating goodness of fit. On the other hand, the SRMR value was close to but higher than the acceptable scores. This result may be related with the high factor load of the eighth item, which had low average and path coefficient. GFI and AGFI scores ≥.90 indicate an acceptable goodness of fit, whereas those scores ≥0.95 refer to perfect goodness of fit (24). The AGFI ≥.80 and the GFI ≥.85 indicate goodness of fit (25). The present study found that the GFI was .86, and that the AGFI was .80, which, in turn, indicated the construct validity of the Turkish version of the APS-POQ-R.

Internal consistency of the findings was analyzed by using Cronbach's alpha coefficient and item–total correlation. Cronbach's alpha coefficient, which measures the homogeneity of the items of a scale, is generally considered as the best indicator of reliability (22). Cronbach's alpha coefficient for the APS-POQ-R was .91 and ranged between .50 and .95 for the subscales of the APS-POQ-R (Table 4). This finding suggests that the internal consistency of the first four subscales of the APS-POQ-R is significantly high. The original APS-POQ-R had a Cronbach's alpha of .86, which ranged between .63 and .83 for its subscales (12). The analysis of the adaptations of the APS-POQ-R reveals that the Chinese version of the APS-POQ-R had a Cronbach's alpha coefficient of .73, with the values that ranged between .49 and .82 for the subscales (15). Cronbach's alpha coefficients of the scale and subscales of the APS-POQ-R were .13 and .86 for the Icelandic version (16) and .67 and .63–.74 for the Australian

version (13), respectively. Moreover, Cronbach's alpha coefficient for the perceptions of care of the Australian version of the APS-POQ-R was .72 (13). The review of the cross-cultural literature adaptation studies suggests that the coefficient for this subscale changed according to the sample and culture. Except for the perceptions of care subscale, the Turkish version of the APS-POQ-R had high Cronbach's alpha coefficients. Low reliability of the perceptions of care subscale is closely related with the fact that the eighth item in the APS-POQ-R is not widely practiced in Turkey so that it decreases internal consistency. Additionally, the characteristics of the sample, cultural differences, and differences in healthcare services may be other reasons.

The present study found that the Turkish version of the APS-POQ-R is a reliable and valid measurement tool to evaluate the patient scores and pain management quality for patients who underwent surgical operation and for nursing process planning. Further research is warranted to better understand the perceptions of care subscale using a larger sample size. Additionally, the Turkish version of the APS-POQ-R may be used to test the efficiency of the attempts to improve pain management quality.

Ethics Committee Approval: Ethics committee approval was received for this study from Eastern Mediterranean University ethics committee. (Approval Date: 04.11.2016, Approval Number: ETK00-2016-0156).

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

Peer-review: Externally peer-reviewed.

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Original Article

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Analyzing the Overuse of Magnetic Resonance Imaging for Musculoskeletal Disorders

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BACKGROUND/AIMS
The overuse of healthcare is a growing concern worldwide. Magnetic resonance imaging (MRI) is an important diagnostic tool for the spectrum of healthcare providers who treat musculoskeletal (MSK) conditions. The aim of the present study was to demonstrate the overuse of MRI in MSK system imaging.

MATERIAL and METHODS
MSK MRIs that were conducted between December 31, 2016 and May 1, 2019 in our hospital were systematically selected. MRIs were divided into groups by anatomical regions. All MRI reports were reviewed according to the findings by two orthopedic surgeons and recorded as normal, abnormal, and insignificant. The number of MRIs was determined according to the departments. Descriptive statistics were performed by using SPSS 22.0.

RESULTS
In total, 2413 MRI reports were detected and scanned. The mean age of the patients was 49.5 years. The lumbar was the most frequent region that had been evaluated by MRI. Of the 2413 MRI reports, 7.54% had normal findings, whereas 26.64% had insignificant findings. In addition, 65.82% of the MRI reports had abnormal findings.

CONCLUSION
The overuse of MRI is a serious health problem that leads to an increase in costs. Constitution of appropriate guidelines and education of patients may facilitate a decrease in MRI requests.

Keywords: Imaging, magnetic resonance imaging, musculoskeletal, overuse

INTRODUCTION

Magnetic resonance imaging (MRI) is a medical imaging device that has been used since the early 1980s (1). MRI is a very important diagnostic tool for imaging the musculoskeletal (MSK) system. It continues to be the standard of care for imaging ligament, cartilage, and intraosseous abnormalities. It has a matchless skill display high-resolution anatomy images noninvasively. This has made MRI the preferred imaging technology for detecting pathologies in soft tissues, such as meniscal, ligament, and tendon tears, and in occult bone injuries (2, 3).

It has been revealed that factors, such as hospital physicians to population ratio, MRI units to population ratio, and the financial situation of the family, may all affect MRI usage (4).

Excessive utilization of healthcare, especially MRI, is becoming increasingly problematic (5, 6).

Magnetic resonance imaging has the obvious advantage of having an absence of radiation, but the disadvantages include higher costs, less availability than computerized tomography, and intolerance among young children (7).

The aims of the present study were to determine the extent to which the MRIs of the MSK system were taken in our hospital during a certain period and to detect the percentage of performed MRIs that helped with diagnosis.

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MATERIALS and METHODS

This study was conducted in Kyrenia University. The study protocol was approved by the ethics committee of Kyrenia University. Data were collected from the Picture archiving and communication systems. Since the study was retrospective in nature, informed consent was not obtained.

We systematically selected MSK MRIs from December 31, 2016 to May 1, 2019. All images were performed using a 3T MRI machine (Magnetom Skyra; Siemens, Erlangen, Germany). MRIs were divided into groups by anatomical regions, such as ankle, foot, elbow, knee, wrist, hand, hip, arm, crus, lumbar, shoulder, sacroiliac, cervical, femur, and thoracic. All MRI reports were reviewed by two orthopedic surgeons and recorded as normal, abnormal, and insignificant (Table 1). MRI reports indicating no anatomical or physiological abnormality were recorded as "normal." Reports indicating abnormal findings that caused either medical or surgical treatment were recorded as "abnormal." Minimal abnormalities that were clinically insignificant and did not require further interventions were recorded as "insignificant." The number of MRIs was determined according to the departments.

Statistical Analysis

Descriptive statistics were performed by using Statistical Package for the Social Sciences 22.0 (SPSS IBM Corp.; Armonk, NY, USA) software program.

RESULTS

A total of 2413 MRI reports were detected and scanned. Of the total patient population, 52.55% were female. The mean age of the patients was 49.5 years. The lumbar was the most frequent region that had been evaluated by MRI.

Of the 2413 MRI reports, 7.54% had normal findings, whereas 26.64% had insignificant findings, and 65.82% had abnormal findings (Table 1).

Approximately 1 in 4 (25.4%) of all MRIs were requested by the orthopedic department, and >1 in 3 were requested by the radiology department. The most requested MRI region was the lumbar region with 782, whereas the second most requested MRI region was the knee (Table 2). Approximately 73.4% of the MRI scans were ordered by the radiology, orthopedics, and neurosurgery departments, with 35.7%, 25.4%, and 12.3%, respectively (Table 2) (Figure 1).

TABLE 1. The number of MRI findings by anatomical regions

	Ankle	Foot	Elbow	Knee	Wrist	Hand	Hip	Arm	Crus	Lumbar	Shoulder	Sacroiliac	Cervical	Femur	Thoracic	Total	Total (%)
Normal	6	5	0	31	5	1	27	2	1	18	14	7	36	10	19	182	7.54
Abnormal	46	24	7	256	9	11	43	8	15	639	207	8	263	9	43	1588	65.82
Insignificant	33	25	3	217	17	10	34	2	5	125	58	5	75	7	27	643	26.64
Total	85	54	10	504	31	22	104	12	21	782	279	20	374	26	89	2413	100

MRI: magnetic resonance imaging

TABLE 2. The number and total percentage of MRI types requested by different departments

MRI type	Orthopedics	Neurosurgery	Physical medicine	Emergency	Radiology	Neurology	Others	Total
Ankle	31	0	6	9	36	0	3	85
Foot	16	0	3	4	27	0	4	54
Elbow	5	0	1	0	3	0	1	10
Knee	212	2	21	15	226	0	28	504
Wrist	18	0	2	0	10	0	1	31
Hand	8	0	4	1	8	0	1	22
Hip	35	2	19	2	41	0	5	104
Arm	3	0	1	0	7	0	1	12
Crus	7	0	1	1	9	0	3	21
Lumbar	105	193	96	39	259	28	62	782
Shoulder	132	2	24	8	88	1	24	279
Sacroiliac	3	3	9	0	1	0	4	20
Cervical	26	84	48	21	107	66	22	374
Femur	6	0	0	2	14	0	4	26
Thoracic	5	12	10	1	25	26	10	89
Total (N)	612	298	245	103	861	121	173	2413
Total (%)	25.4%	12.3%	10.1%	4.3%	35.7%	5.0%	7.2%	100%

MRI: magnetic resonance imaging

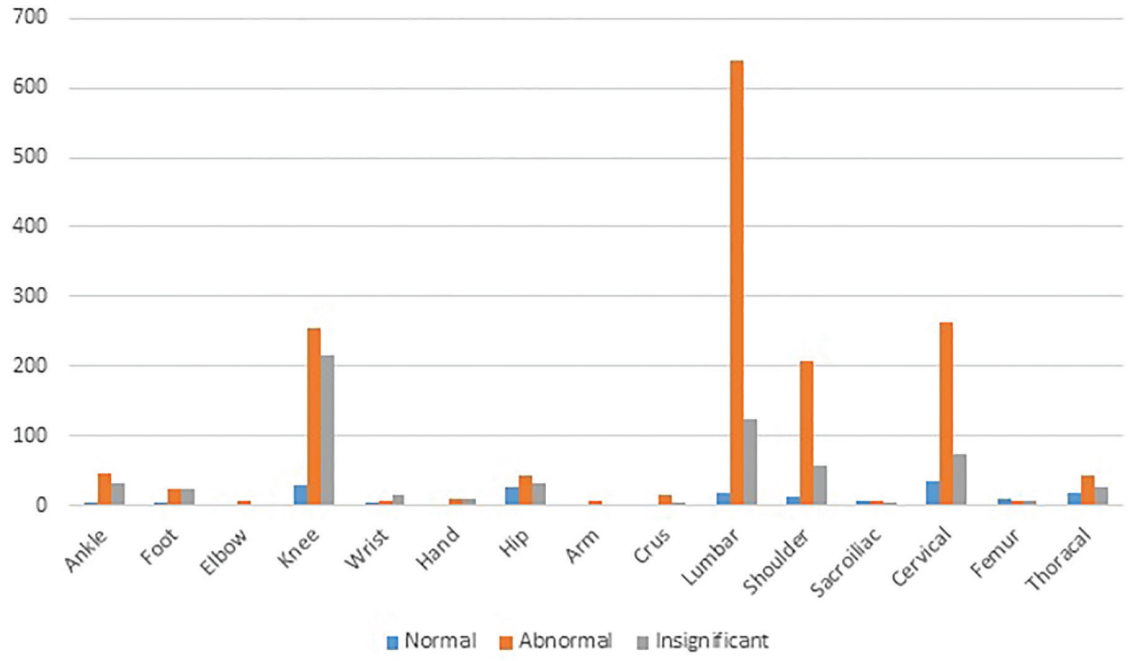

FIGURE I. Anatomical distribution of MRI findings

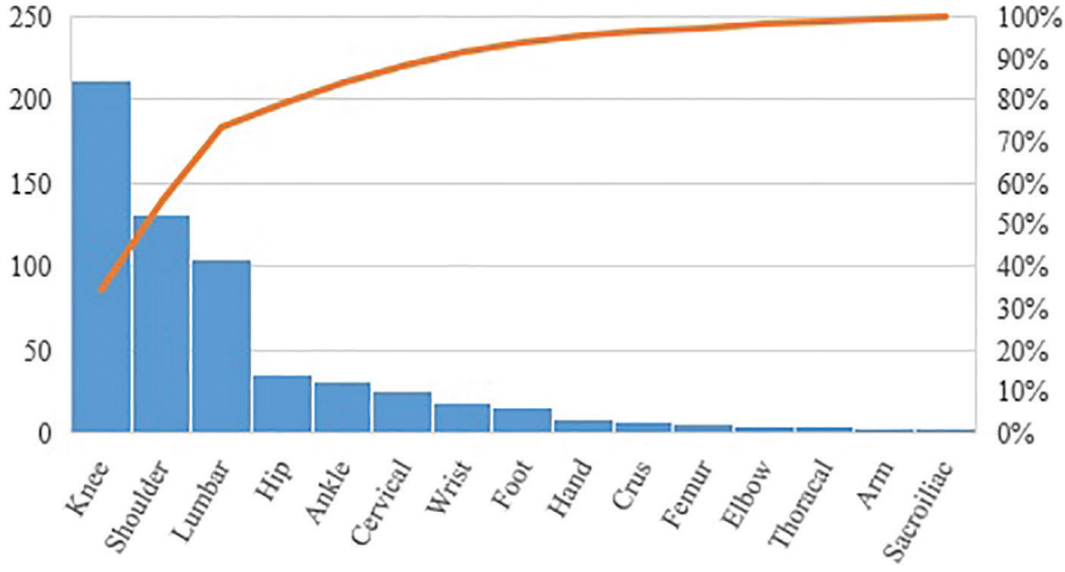

FIGURE 2. Type of MRI requested by the orthopedics department

The most requested MRI by the orthopedics department was the knee with 34.6% (Figure 2).

DISCUSSION

The population characteristics and the existing health system in our country allow the overuse of MRI. In our study, we attempt to consider this fact and to demonstrate the usefulness of the MRIs. For this purpose, the reports of MSK MRIs performed in our hospital for a period covering approximately 2.5 years were reviewed retrospectively. The MRI orders of different departments were examined, and the regions requested for MRIs were also determined. However, the ratio of different department requests has not been investigated.

In our study, when the total number of MRIs was examined, it was found that only a small portion of them had normal findings (7.54%); however, this rate was higher in MRIs for certain regions. For example, we found that approximately 38.5% and

35% of MRI reports were normal for the femur and sacroiliac, respectively.

In our study, we have found that the radiology, orthopedics, neurosurgery, and physical therapy departments had the highest number of MSK MRI requests. More than 1 in 3 of these MRI requests consisted of radiology requests.

The reason for this might be that our hospital has the only 3.0 Tesla MRI in the country. Therefore, the requests of doctors in other centers are ordered by the radiology department to be enforced in our hospital.

Studies on MRI overuse are available in the literature. The overuse of MRI for headaches and migraines has been reported in the literature. In these studies, normal MRI findings were found in more than half of the adult patients with headache (8-10).

In our study, we did not differentiate the requested MRIs according to the symptoms. We only searched the percentages and the number of the findings by departments according to the requested regions.

Normal findings were higher in the femur, hip, and thoracic regions, but lower in other regions. However, when all regions were evaluated, insignificant findings were the least in the lumbar region, whereas in other regions, we found that the number of insignificant findings (wrist) increased >50% (Table 1). The highest abnormal rate appeared in relation to lumbar MRI. However, these findings may be incidental because the correlation between lumbar spine MRI findings and clinical signs and symptoms is poor (11).

In some regions, abnormal findings are equal to the sum of normal and insignificant findings, which may be attributed to non-branch requests. The majority of MSK MRIs consist of the knee and lumbar regions. Insignificant findings, such as bulging discs, discs protrusions in lumbar MRIs, such as bone marrow edema, meniscal, and cartilage signal changes, and fat pad edema, and tendinopathy in knee MRIs, are more common. In our study, MRI findings of symptomatic patients who were admitted to the outpatient clinic were examined, and high rates of positive MRI findings could be seen, even in asymptomatic athletes (12, 13). Insignificant findings were observed in 67.4% of asymptomatic soccer players and 88.9% of kangoo jumpers. These insignificant findings in the MRI reports disturbed the patients and their relatives. All patients should be informed about these insignificant findings by the physician.

In fact, a reason for the overuse of MRI may be the insistence of patients to have an MRI. Awareness of the absence of radiation increases referrals to hospital, especially for patients with high income. However, physicians' medical concerns could also support the overuse of MRI. Patients are often afraid of their symptoms and unfounded comments made by people around them. This fear leads them to demand an MRI from their doctor. With a good physical examination and subsequent disclosure of symptoms to the patient, the majority of patients believe that these demands are unwarranted (14). A good patient–physician relationship and informing the patients is the only way to prevent the overuse of MRI as a result of patient anxiety caused by their symptoms. Considering these factors, further studies may reveal more detailed and enlightening information.

Clinical negligence claims and litigations are constantly increasing. According to the National Health Service statistics in the United Kingdom, the most common cause of claims against orthopedic surgeons is postoperative complications, whereas the second most common cause is wrong, delayed, or failure diagnosis (15). The fact that wrong, delayed, or failure diagnosis is so high in medical litigations leads doctors to conduct more defensive medicine practice. In a web-based survey of 1214 orthopedic surgeons in the USA, 96% of surgeons reported that they practiced defensive medicine by ordering laboratory, imaging, consultation, and hospital admissions to avoid possible litigations. On average, 24% of all tests were reported to be for defensive reasons (16). In our study, normal results (7.54%) and most of the insignificant results (26.64%) may have been ordered due to the practice of defensive medicine.

Kung et al. (4) concluded that factors, such as hospital physicians to population ratio, MRI units to population ratio, and financial situation of the family, may all affect MRI usage. Our hospital is situated in a low populated area, and the MRI units to population ratio is also high. However, the income and socioeconomic status of the families living in the region in which the hospital is located is high compared with the country in general.

Saadat et al. (17) conducted a survey among private MRI centers in Tehran to study the proportion of MRI scans that resulted in significant clinical findings. Of all the MRI reports, 17.2% had normal findings, whereas 54.6% had abnormal findings. Approximately 28% of the reports had indicated substantial changes. In our study, of all the MRI reports, 7.54% had normal findings, whereas 65.82% had abnormal findings, and 26.64% had insignificant findings.

Our study has a limitation. We investigated each department only with respect to the region of MRI that was requested. However, we did not analyze the MRI findings according to departments. This may be the subject of a different study.

The overuse of medical interventions, such as MRI, is an important problem that leads to excessive costs and can have serious consequences. Constitution of appropriate guidelines and education of patients may facilitate a decrease in MRI requests.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kyrenia University (2019/01-002).

Informed Consent: Since this was a retrospective study, informed consent could not be taken from the patients.

Peer-review: Externally peer-reviewed.

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

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Original Article

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Prognostic Value of the Uric Acid Level and Its Effect on Survival in Stage I–III Gastric Cancer

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BACKGROUND/AIMS
Uric acid is the product of purine metabolism. In this study, we investigated the prognostic value of serum uric acid value on disease-free and overall survival (DSF and OS) in gastric cancer.

MATERIAL and METHODS
The records of 110 patients who underwent surgery for Stage I–III gastric cancer between 2012 and 2014 were retrospectively analyzed.

RESULTS
The average follow-up period was 42 months in 110 patients studied. The mean age was 63.7±11.6 years. Seventy percent of patients were male, and 43% underwent total and 57% subtotal gastrectomy. Most of gastric tumors were located in the distal stomach (56%), 24% in cardia, and 19% in corpus. While the tumor size was found to be larger than 4 cm in 60% of the patients and larger than 8 cm in 20%, according to the TNM system, 11% were Stage I , 29% Stage II, and 60% Stage III. Metastatic/excised lymph node ratio is <0.3 in 59% of patients. The mean uric acid level was 4.63±1.44. The cut-off values of uric acid were studied as 4 and 6.

CONCLUSION
When the mean distribution of the OS and DFS values according to uric acid groups was examined, there was no statistically significant difference between the groups (p>0.05). In our study, while the uric acid value was not found to be effective in DSF and OS, the stage, metastatic lymph node ratio, tumor size, and localization were found to be effective factors in OS.

Keywords: Disease-free survival, gastric cancer, overall survival, serum uric acid

INTRODUCTION

Uric acid emerges as the final enzymatic product in the breakdown of purine nucleotides and is found free in humans and great apes. The purine catabolism in humans is the shortest one among vertebrates. Urate oxidase enzyme that converts uric acid to allantoin mutates in two steps. In other mammals, the end product of purine metabolism is allantoin, and it is eliminated by urine (1, 2). As a nucleic acid turnover product, uric acid increases rapidly in the growing diseased tissues of cancer patients (3). Therefore, it might be a prognostic marker in cancer patients. To the best of our knowledge, there are no studies in the literature examining the relationship between gastric cancer and serum uric acid value (SUA) in many years (4). In this study, we investigated the prognostic value on SUA on DF and OS in gastric cancer.

MATERIALS and METHODS

The records of 110 patients who underwent curative surgery (total/subtotal gastrectomy+D2 lymph node dissection) for Stage I–III stomach cancer between 2012 and 2014 and followed-up regularly were retrospectively analyzed. Patients with Gout's disease Gout, Stage IV patients treated with palliatively or with additional organ resection, histological types other than epithelial tumors, patients treated with neoadjuvant chemotherapy, emergent cases, patients who needed blood product transfusion in the perioperative period, patients that could not complete adjuvant therapy, and patients with preoperative infection were excluded from the study, because in these cases, SUA has already increased due to its anti-inflammatory properties.

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Patients were evaluated by medical oncology and radiotherapy specialists after the operation and received the necessary adjuvant treatments. Control examinations were held once every 3 months for the first 2 years of surgery and every 6 months for the following 3 years.

Other than history and physical examination, complete blood count, biochemical assays, and tumor markers (CEA, Ca 19-9) were studied at each control. Abdominal ultrasonography, computed tomography (CT), or upper gastrointestinal (GIS) endoscopy was performed in accordance with the patients' complaints. Abdominal radiologic imaging was performed once a year in patients with no complaints or examination findings. The age, gender, blood group, type of operation, pathology, tumor size, the number of pathologic lymph and total lymph nodes, and the TNM stage were recorded. Peripheral blood samples were collected approximately 2 weeks before surgery, and SUA values were recorded.

Ethics committee approval was received for this study from the local ethics committee of Dr. Abdurrahman Yurtaslan Training and Research Hospital (AOH 2017/10/17). Written informed consent was obtained from patients who participated in this study.

Statistical Analysis

Statistical calculations were performed using the Statistical Package for the Social Sciences for Windows v 16.0 (SPSS Inc.; Chicago, IL, USA). Fisher's exact test, Pearson's chi-squared, and Mann–Whitney U analysis were used. The level of significance was set at $p<0.05$.

RESULTS

The average follow-up duration of 110 patients was 42 months, and the general characteristics are summarized in Table I. The mean age was 63.7±11.6 years. Seventy percent of the patients were male, and 43% underwent total and 57% subtotal gastrectomy. Most of gastric tumors were located in distal stomach (56%), 24% in cardia, and 19% in corpus, and 75% were reported as adenocarcinoma, 19% signed cell carcinoma, and 3% mucinous carcinoma. While the tumor size was found to be >4 cm in 60% of the patients and >8 cm in 20%, according to the TNM system, 11% were Stage I, 29% Stage II, and 60% Stage III. The mean uric acid level was found to be 4.63±1.44. The cut-off values of uric acid were studied as 4 and 6.

When the distribution of categorical variables according to the survival of cases is examined, there was a statistically significant difference between the groups in terms of the surgery type, tumor size, lymph node ratio, and disease stages ($p<0.05$).

There was no statistically significant difference between the groups in terms of other variables ($p>0.05$) (Table 2). Two different cut-off values as 2–4 and >4 and 2–6 and >6 were studied for uric acid levels. In both values, the uric acid levels had no a significant effect on OS and DFS (Table 3).

DISCUSSION

Uric acid occurs when the hypoxanthine and xanthine, which are the digestive consequence of foods and beverages containing purine nucleoside in physiological pH, enter the enzymatic reaction with xanthine oxidoreductase (5). According to the hypothesis of Ames et al. (6), the increase in the level of uric acid in the blood gives an advantage to human beings.

TABLE I. Demographic and clinical characteristics of cases

		n	%
Gender	Female	33	30
	Male	77	70
Uric acid 4	2–4	38	34.5
	>4	72	65.5
Uric acid 6	2-6	94	85.5
	>6	16	14.5
Age 50	≤50	13	11.8
	>50	97	88.2
Age 70	≤70	74	67.3
	>70	36	32.7
Surgery type	Total gastrectomy	47	42.7
	Subtotal gastrectomy	63	57.3
Pathology	Adenocarcinoma	83	75.5
	Mucinous	3	2.7
	Signet cell	21	19.1
	Diffuse	3	2.7
Localization	Cardia	26	23.6
	Corpus	21	19.1
	Antrum	61	55.5
	Whole	2	1.8
Size 4	≤4 cm	45	40.9
	>4 cm	65	59.1
Size 8	≤8 cm	88	80
	>8 cm	22	20
Ratio 0.30	≤0.30	66	60
	>0.30	44	40
Ratio 0.60-0.90	≤0.60	90	81.8
	>0.60	20	18.2
Stage	I	12	10.9
	II	32	29.1
	III	66	60
		Mean±SS	**Median (Min.–Max.)**
Age		63.71±11.69	63 (34-85)
Uric Acid		4.63±1.44	4.45 (2.1-11.2)
Tm size		5.68±3.12	5 (0.5-15)
Metastatic LN		5.98±6.87	3 (0-30)
Total LN		18.42±8.3	18 (2-40)
LN ratio		0.29±0.29	0.19 (0-0.9)
OS		23.84±17.44	22.5 (1-62)
DFS		22.47±17.67	16 (1-62)

OS: overall survival; DFS: disease free survival; LN: lenf node

TABLE 2. Distribution of categorical variables according to survival status of cases

		Exitus		Surviving			
		n	%	n	%	X^2	p
Gender	Female	19	29.2	14	31.1	0.045	0.832
	Male	46	70.8	31	68.9		
Uric acid 4	2–4	23	35.4	15	33.3	0.049	0.824
	>4	42	64.6	30	66.7		
Uric acid 6	2-6	55	84.6	39	86.7	0.090	0.764
	>6	10	15.4	6	13.3		
Age 50	≤50	5	7.7	8	17.8	2.595	0.107
	>50	60	92.3	37	82.2		
Age 70	≤70	39	60	35	77.8	3.817	0.051
	>70	26	40	10	22.2		
Surgery type	Total gastrectomy	36	55.4	11	24.4	10.402	0.001
	Subtotal gastrectomy	29	44.6	34	75.6		
Pathology	Adenocarcinoma	48	73.8	35	77.8	0.266	0.966
	Mucinous	2	3.1	1	2.2		
	Signet cell	13	20	8	17.8		
	Diffuse	2	3.1	1	2.2		
Localization	Cardia	21	32.3	5	11.1	10.947	0.007
	Corpus	14	21.5	7	15.6		
	Antrum	28	43.1	33	73.3		
	Whole	2	3.1	0	0		
Size 4	≤4 cm	18	27.7	27	60	11.482	0.001
	>4 cm	47	72.3	18	40		
Size 8	≤8 cm	47	72.3	41	91.1	5.876	0.015
	>8 cm	18	27.7	4	8.9		
Ratio 0.30	≤0.30	32	49.2	34	75.6	7.678	0.006
	>0.30	33	50.8	11	24.4		
Ratio 0.60-0.90	≤0.60	47	72.3	43	95.6	9.661	0.002
	>0.60	18	27.7	2	4.4		
Stage	I	2	3.1	10	22.2	24.140	0.001
	II	12	18.5	20	44.4		
	III	51	78.5	15	33.3		

TABLE 3. Mean distribution of OS and DFS values according to uric acid groups

	Uric Acid	Mean ± SS	Median (Min.-Max.)	Z	p
OS	2-4	24.76±14.69	24.5 (2-45)	-	0.513
	>4	23.35±18.81	20.5 (1-62)	0.655	
DFS	2-4	22.34±15.44	17 (2-45)	-	0.617
	>4	22.54±18.85	16 (1-62)	0.500	
OS	2-6	24.51±17.28	24.5 (1-62)	-	0.535
	>6	19.88±18.47	12 (1-45)	0.620	
DFS	2-6	22.95±17.61	19 (1-62)	-	0.671
	>6	19.69±18.38	11.5 (1-45)	0.424	

OS: overall survival; DFS: disease-free survival

As shown in the in vitro experiments, uric acid has antioxidant properties by eliminating singlet oxygen, peroxyl radicals, and hydroxyl radicals.

This reaction of uric acid with oxidants can cause cell damage by leading to the formation of other radicals, and this creates a paradox whether it is oxidant or antioxidant. Elevated uric acid levels can cause hypertension, obesity, type 2 diabetes, dyslipidemia, renal damage, and cancer (6, 7). In the study by Kolonel et al. (3) solely on male subjects, while the uric acid level was found to be unrelated to stomach, colon, rectum, lung, bladder, and hematopoietic system cancers, high SUA levels were associated with prostate cancer. As a nucleic acid turnover product, uric acid increases rapidly in the growing diseased tissues of cancer patients, and this may lead to hyperuricemia. SUA with an antioxidant property rich in blood is a free radical scavenger that cleans metal ions (8, 9). Uric acid activates proinflammatory cytokines such as extracellular signal-regulated kinase, mitogen-activated protein kinases, cyclooxygenase-2, and platelet-derived growth factor. It was shown *in vivo* studies in rats that increased uric acid levels are associated with vascular injury, which has been shown to cause renal damage and hypertension (10-12). As uric acid may cause hyperuricemia in cancer patients, it may also increase secretion from the kidneys due to damage to the tubules or tumor-related factors and may lead to hypouricemia (3). Increased SUA also lead to cardiovascular, respiratory, and renal diseases and metabolic syndromes (13, 14). Increased SUA values strengthen the inflammatory response and show both oxidant and antioxidant properties and trigger many diseases, from gout to cancer. It is claimed in cancer that it is effective in increased cell turnover and tumor lysis syndrome (15-17). While low SUA levels damage neurons, high levels provide neuroprotection by contributing to inflammation. Because of its antioxidant effects, SUA has been claimed to protect against cancer. However, studies on cancer and cancer-related mortality are showing contradictory results. While Kuo et al. (18) claim that low SUA levels are associated with cancer-related mortality, Strasak et al. (19) showed that a high SUA level is an independent risk factor for total cancer mortality (15). The relationship between cancer and SUA is complex. In their most recent meta-analysis, Dovell et al. (20) emphasized that the increase in SUA values is related to cancer. In a study of 16,000 Swedish patients with gout, it has been observed that an increased uric acid level increases the incidence of oral cavity, pharynx, colon, liver, bile duct, pancreas, lung, skin (melanoma, nonmelanoma), endometrium, and renal cancers (21). Cetin et al. (22) suggested that high SUA levels in Stage IIIA and IIIB colorectal cancer patients may lead to early metastasis. Although Taghizadeh et al. (23) suggest that high SUA levels lead to low cancer mortality, other studies have shown that increased SUA is an independent risk factor for mortality (19, 24, 25).

In this study, we investigated the prognostic value of SUA on DFS and OS in Stage I–III gastric cancer. In our study, both hyperuricemic and hyporuricemic SUA values were not found to be a prognostic factor in Stage I–III stomach cancer. Its impact on both DFS and OS is not statistically significant. There have not been specific studies in the literature for the relation between gastric cancer and SUA in many years, since 1946. In this

sense, to the best of our knowledge, our work is the first in the literature, and extensive prospective randomized studies are required to explore this issue further.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Dr.Abdurrahman Yurtaslan Training and Research Hospital (AOH 2017/10/17).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Original Article

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Basic First Aid Knowledge Levels of Students of the Vocational School of Health Services

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BACKGROUND/AIMS
In this descriptive study, our aim was to evaluate the knowledge on basic first aid of students attending the Vocational School of Health Services.

MATERIALS and METHODS
The study group consisted of 296 students in 23 departments of the Vocational School of Health Services. A total of 31 questions administered via the Students Introductory Information Form and Basic First Aid Questionnaire were answered by students who agreed to participate voluntarily in the research. The analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Version 13.0 (IBM Corp.; Armonk, NY, USA) package program in the computer environment with a p-value <0.05 determining the significance level.

RESULTS
It has been determined that 88.9% of the students had previously received basic education on first aid, and 50% of the students believed that their knowledge in this area was sufficient. The basic first aid knowledge score of the students was calculated as 76.03. The most correctly answered question was regarding the definition of basic first aid, while the least correctly answered question was on the chest compression rates.

CONCLUSION
In addition to theoretical courses, if time spent practicing with models in applied courses is not sufficient; it can prevent the students from reinforcing their knowledge. However, in addition to applications during the internship training, professional practice can help the students to acquire the required knowledge.

Keywords: Education, first aid, health services, knowledge

INTRODUCTION

In cases involving accidents or life-threatening emergencies, first aid means that a person (or persons) at the scene provides medical assistance without any medications to save the victims life and/or to prevent the situation from getting worse until the professional health workers arrive at the scene (1-6). In cases when first aid is required, a successfully applied first aid intervention can be lifesaving (3). At any moment in life, an unexpected situation may happen, involving an accident or illness that could require first aid. In such cases, there may not be professional health workers at the scene. In these emergency situations, a health worker may not be immediately available to provide assistance, which means that a member of the public may have to provide first aid in case of an accident or injury, and anyone familiar with the principles of first aid could provide assistance (7). The ability to administered first aid to oneself or to another person is very important because it can contribute to increased survival rates, the prevention of injury, and the healing process (2). Considering all these situations, individuals who provide first aid apply life saving measures until emergency health workers reach the scene, and they play an important role in emergency health services (3).

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As the locations in which accidents requiring first aid happen are frequently crowded, it is natural to assume that universities are among these environments. Although first aid lessons are a compulsory part of the curriculum in the faculties and schools providing health-related education, the number of studies on whether the theoretical and/or practical knowledge levels of the students receiving first aid lessons/education are sufficient is limited (1, 2). In fact, it is important that individuals understand and practice first aid, which can be beneficial for them, their relatives, and even society (3).

The aim of this study was to evaluate the theoretical knowledge level of second-grade students attending the Vocational School of Health Services of a private university in the Turkish Republic of Northern Cyprus. The answers were sought to the following research questions:

I. What is an average score of the students' knowledge about basic first aid?
II. Is there a difference on basic first aid knowledge levels between the basic first aid course and the students taking courses and not taking courses?
III. What are the differences between the students who find their knowledge in first aid to be sufficient and those who feel that they are lacking it?

MATERIAL and METHODS

The research population consisted of 296 second-grade students attending the Vocational School of Health Services of a private university in the Turkish Republic of Northern Cyprus during the 2017–2018 spring semester. In the descriptive study, the sample selection was made by choosing 50% of students, and all participants were reached.

Prior to the study, written permission was obtained from the Directorate of Vocational School of Health Services and from the Ethics Review Board (Near East University Scientific Research and Ethics Committee, 31.05.2018/607). Verbal consent was obtained from the students who accepted to participate voluntarily in the data collection stage.

Data were collected by the researchers using the Student Introductory Information Form and basic first aid questions developed in accordance with the literature. In the Student Introductory Information Form, 10 questions on socio-demographic characteristics such as age and gender, education on basic first aid, participation in activities within the university and/or external, basic first aid practice situation and self-sufficiency in relation to basic first aid were asked.

A total of 21 questions were asked about basic first aid. The questions included the definition of the subject, adult and child basic life support, respiratory blockages, positions, bleeding, fractures, dislocations and sprains, epileptic seizures, penetrating and cutting tool injuries, burns, freezing, tourniquet application, security measures, animal bites, insect stings, and limb ruptures.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 13.0 (IBM Corp.; Armonk, NY, USA). Pearson's chi-squared test and Fisher's exact test were used to compare the number of correct answers among students. A p-value <0.05 was considered significant.

RESULTS

The mean age of 296 students was 21.91±2.41; 36.1% (n=107) were female, and 63.9% (n=189) were male. In Table 1, it can be seen that 88.9% of the students received basic first aid education. It was found that the ratio of students who found their knowledge to be sufficient in basic first aid was equal to the ratio of students who found their knowledge to be insufficient (n=148; 50%; in both groups).

In our study, the mean first aid score of the students was evaluated. Accordingly, it was determined that their basic first aid knowledge point average was 76.03. When the average score of basic first aid knowledge according to gender is examined, it is found that females had a score of 76.46, and the score of males was 75.79. While the average knowledge score of the students who were previously trained about basic first aid was 76.01, it was determined that the average score of the students who found their knowledge to be sufficient was 77.47 (Table 2).

Table 3 shows the correct and incorrect response rates of the subjects whose basic first aid knowledge was examined. While the ratio of answering the questions is high, the issues of chest compressions, airway obstruction, tourniquet application, and shock position had the highest number of incorrect answers.

TABLE 1. Descriptive properties (n=296)

Descriptive properties	(n)	(%)
Taking basic first aid education		
Yes	263	88.9
No	33	11.1
Finding one's knowledge sufficient about basic first aid		
Yes	148	50%
No	148	50%

TABLE 2. Info points averages

Basic first aid knowledge average score	n	Mean score
Knowledge point average by gender		
Woman	107	76.46
Man	189	75.79
The average knowledge score for the students who were trained and not trained in basic first aid		
Yes	263	76.01
No	33	76.19
The average knowledge score of the students who find themselves sufficiently knowledge able regarding basic first aid		
Yes	148	77.47
No	148	74.58

TABLE 3. Correct answer rates for basic first aid questions

	True		False	
Basic first aid questions	**n**	**%**	**n**	**%**
Definition of basic first aid	288	97.3	8	2.7
Chest compression rates	64	21.6	232	78.4
Baby consciousness control	241	81.4	55	18.6
Respiratory tract blockages	121	40.9	175	59.1
Coma position	236	79.7	60	20.3
External bleeding	266	89.9	30	10.1
Fractures, dislocations, and sprains	226	76.4	70	23.6
Epileptic seizure	277	93.6	19	6.4
Penetrating, cutting tool injuries	264	89.2	32	10.8
Burn	230	77.7	66	22.3
Tourniquet application	95	32.1	201	67.9
Nasal bleeding	252	85.1	44	14.9
Freezing	276	93.2	20	6.8
Safety precautions	271	91.6	25	8.4
Safe zone	254	85.8	42	14.2
Animal bites, insect stings	221	74.7	75	25.3
Shock position	102	34.5	194	65.5
Limb ruptures	253	85.5	43	14.5
Pediatric cardiac massage	285	96.3	11	3.7
Chest compression/artificial respiration rates	235	79.4	61	20.6
Artificial respiration	269	90.9	27	9.1

TABLE 4. Distribution of basic first aid questions in students who find their knowledge about first aid sufficient/insufficient

	Sufficient		Insufficient		
Basic first aid question	**True**	**False**	**True**	**False**	**p**
Baby consciousness control	131	17	110	38	0.002
Animal bites, insect stings	120	28	101	48	0.011
Chest compression/artificial respiration rates	127	21	108	40	0.006

TABLE 5. Accurate response rates for basic first aid questions given by gender

	Women		Men		
Basic first aid question	**True**	**False**	**True**	**False**	**p**
External bleeding	105	2	161	28	0.00
Nasal bleeding	99	8	153	36	0.007

In Table 4, the rates of students who did not find their knowledge about first aid sufficient/insufficient according to these data, there was a statistically significant difference in the topics covering the baby consciousness control, animal bites, insect bites, and chest compression/artificial respiration rates ($p<0.05$).

Table 5 shows the rates that differed significantly in the answers of students evaluated according to their gender. Thus, there was a statistically significant difference in relation to external bleeding and nose bleeding ($p<0.05$).

DISCUSSION

Similar to the results of a study conducted to determine the level of knowledge and factors affecting the basic first aid knowledge in a vocational school of health services students, in our study, the rate of correct answers to 21 questions asked to measure the knowledge level of the students about basic first aid was highly correct (2). In the results of a study conducted on medical students, it was determined that the students did not respond correctly to all questions about first aid (8, 9). In our results, it was found that there was a lack of information about these subjects based on the students' incorrect answers to questions regarding basic first aid, including the rate of chest compressions applied per minute in the active heart massage, first aid in respiratory tract obstructions, tourniquet application, and the shock position. As stated by Büyükkayacı Duman et al. (1), it is thought that students lack knowledge in relation to some questions, and this means they cannot fully comprehend the situation/event. In the study on the first aid knowledge levels of class teachers, it was found that 95.9% of the teachers did not know how to perform cardiac massage (7). According to the findings of a similar study, university students have serious shortcomings in basic subjects such as chest compression and artificial respiration. The reason for this is the absence of courses with the first aid content in the departments outside the health sector. In our study, the most incorrectly answered question was determined as the one related to the rate of chest compression for an effective cardiac massage. The research universe comprised students attending a vocational school of health services. Therefore, this indicates that the rate of chest compression requires more practice and observation rather than theoretical information.

In studies conducted on different audiences, such as a police school, vocational school students, and non-physicians, basic first aid was the most correctly answered question in the research conducted by different researchers (96.7%, 88.2%, 91.8%) (2, 10, 11). According to the results of our study, the basic first aid definition question was answered correctly with a rate of 97.3%, which is similar to the literature.

In our study, the average score for the basic first aid knowledge of the students was determined to be 76.03. Similar to the results of our study, in a study that involved the first-year medical students, the average score for basic first aid was 68.0 (9). In contrast to these results, this rate was determined to be 5.96 in a study conducted with forestry and forestry vocational school students (3). This ratio was determined to be 42.42±16.44 in the results of a first aid study on prisoners (12). In the light of the information in the literature, it can be thought that education, and particularly the education received in the field of health, have a significant effect on the first aid knowledge point average. In addition, studies determining the level of first aid knowledge of students, nurses, or policemen are also important to identify educational deficiencies related to first aid.

In a study that examined differences in first aid knowledge according to gender, a higher number of female students correctly answered the statement related to "cuts and dirty wounds are washed with soapy water, and tincture is applied" in comparison to male students. In the same study, in response to a question stating that "for patients poisoned with caustic substances such as bleach or oil, vomiting should be induced immediately," it was

found that females answered this question correctly more frequently (1). According to our study results, the questions that were answered correctly less frequently by both male and female students were related to coma position (p<0.319), fractures, dislocations, and sprains (p<0.443), penetrating and cutting tool injuries (p<0.541), burns (p<0.589), and limb fractures (p<0.235) (Table 3).

A total of 11.1% of students who participated in the research stated that they had not received the first aid training. In a study by Usta et al. (3), 44% of the participants claimed that they had no training, and Nayir et al. (13) determined that teachers had knowledge of first aid, while 61.5% of the participants did not receive first aid training. According to the literature, the number of people who received first aid training in our study is high (88.9%). The reasons of this could be that first aid is a basic and compulsory course in many departments related to vocational schools of health services. The expansion of first aid training will contribute to an increase in the first aid knowledge levels.

This study was limited to the second-year students attending the Vocational School of Health Services. According to the findings obtained from the study, when the average of the students' response to the questions about first aid is taken into consideration, the correct response rates are high for many questions. However, it is important to note that some students also answered them incorrectly. The reasons for these incorrect answers could be that the student was not attending the Vocational School of Health Services and/or had moved from another part of another faculty to the Vocational School.

In non-health departments where first aid courses are not compulsory, it is possible to provide basic first aid training to students. The incorrect answers of students to the basic first questions can be analyzed further to determine what information they are lacking and to take corrective action in a timely manner. Considering that some of the basic first aid questions have been incorrectly answered by the students, it is necessary to examine the problems they have missed and correct them early. In this context, to add the first aid class to the departments that are not obligatory, to increase the interest in the class, to increase the visual and audio materials, to organize first-aid-related seminars such as symposiums and/or courses during the training periods, to increase the basic first aid hours, and to provide students with a certificate of achievement or certifications are important. In addition, it will be possible to increase the awareness of the students regarding the fact that receiving a first aid training in any period of their education will have a direct impact on their knowledge and could potentially save lives.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Near East University Scientific Research and Ethics Committee (31.05.2018/607).

Informed Consent: Verbal informed consent was obtained fromstudents who participated in this study.

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Original Article

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The Factors Affecting Job Satisfaction of Emergency Medical Services Professionals in Ankara

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BACKGROUND/AIMS
The aim of the present study was to determine the job satisfaction level of emergency medical services (EMS) professionals and factors affecting job satisfaction.

MATERIALS and METHODS
The study included 781 EMS professionals in Ankara, Turkey and was conducted from September 2018 to November 2018. A semi-structured questionnaire including socio-demographic data and Minnesota Job Satisfaction Scale was used in the study.

RESULTS
The mean score of internal satisfaction of the participants was 3.4±0.6, whereas the mean score of external satisfaction was 2.9±0.7, and the overall mean score was 3.2±0.6. There was a significant difference between gender and external satisfaction scale score ($p<0.05$). External and general satisfaction scores of female employees were significantly lower than those of male employees.

CONCLUSION
External satisfaction level of EMS professionals is low. Problems related to access to management, participation in management, career opportunities, wages, security, being appreciated, and prevention of violence negatively affect job satisfaction.

Keywords: Emergency medical services, health professionals, job satisfaction

INTRODUCTION

Emergency medical services (EMS) are a labor-intensive work field. The contribution of the professionals working in this field to the quality, efficiency, accessibility, health expenditures, and satisfaction of the service is very important (1, 2). Therefore, maximizing employee performance directly affects the efficiency of the service. Performance is highly influenced by job satisfaction. Employees who are satisfied with their jobs have been shown to be more productive and more committed to their own organizations (1-4).

Job satisfaction can be defined as the emotional response of the individual to the fulfillment of his/her job requirements (physical, psychological, and social) (4-7). Studies have shown that job satisfaction of health professionals is affected by many factors, such as gender, age, education level, work experience, working conditions, salary, working hours, and promotion opportunities (8, 9). In addition to these factors, the characteristics of the work environment also significantly affect job satisfaction (10).

In general, psychological problems, such as stress, fatigue, burnout, and depression, in health services affect job satisfaction and therefore health care systems. The most stressful area in health services is EMS (9-11). Pre-hospital professionals often face many stressors, such as working for long hours, frequent exposure to traumatic events, time pressure, negative weather conditions, serving in insecure environments, and violence. These stressors can lead to reduced job satisfaction over time, burnout, physical and psychological problems, serious labor loss, and abandonment of the profession (11, 12).

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In the studies conducted, it was stated that the burnout levels of the ambulance professionals were high, and that this would affect the patient care and the quality of the service provided (10, 11, 13). Reduction in job satisfaction may be a trigger for many mental problems, such as burnout, anxiety, depression, and suicide (14).

Considering all these factors, it is very important to know the job satisfaction levels of the EMS professionals with respect to increasing the quality and productivity in health services. Although many studies have been conducted on health care professionals, there are few studies on EMS professionals. The aim of the present study was to determine the job satisfaction levels of EMS professionals and the factors affecting job satisfaction.

MATERIALS and METHODS

The study was approved by the ethics committee of Ankara Yıldırım Beyazıt University (date 18/09/2018, no. 41). Written informed consent was obtained from the individuals who participated in the study.

In this descriptive research, the questionnaire technique was used as the quantitative method, and the focus group interview technique was used as the qualitative method.

Participants

The study consisted of health professionals working in ambulances or call center of the EMS in Ankara, Turkey. In the present study, the simple random sampling method was used. The questionnaires were distributed to all health professionals by the researcher, and they were collected after they were answered. The professionals who accepted to fill out the questionnaires voluntarily formed the sample of the study. Of these, 1757 were health professionals (113 doctors; 99 nurses, midwives, or public health technicians; 1131 emergency medical technicians; and 414 paramedics), and 604 were other staff (secretaries, cleaning staff, and drivers, and so on).

The study was conducted on 781 participants from September 2018 to November 2018. The criterion in the sample selection was "volunteering to fill out the surveys." Overall, 755 refused to participate in the study, whereas 221 were unavailable. All the questionnaires and scales used in the study were given to the employees individually, and the questionnaires were delivered to the researchers after completion.

Data Collection Forms

The socio-demographic data form was developed by the researcher as a result of the literature review, whereas the Minnesota Job Satisfaction Scale (MJSS) and semi-structured questionnaire were used in the study.

The socio-demographic data form consists of nine questions on gender, age, marital and educational status, having children, income and occupational data, professional experience, and seniority years in pre-hospital field.

Minnesota Job Satisfaction Scale is a 20-item scale developed by Weiss, David, England, and Lofquist to measure job satisfaction (15). It was translated into Turkish by Baycan; validity and reliability studies were performed (Cronbach's alpha=0.77) (16). It is a 5-point Likert-type scale. There is no inverse question in the scale. The MJSS consists of 20 items that measure the internal, external, and general levels of satisfaction. While the general satisfaction score is the arithmetic mean of all items, the internal satisfaction score is the arithmetic mean of the 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, 7^{th}, 8^{th}, 9^{th}, 10^{th}, 11^{th}, 15^{th}, 16^{th}, and 20^{th} items, and the external satisfaction score is the arithmetic mean of the 5^{th}, 6^{th}, 12^{th}, 13^{th}, 14^{th}, 17^{th}, 18^{th}, and 19^{th} items. The neutral satisfaction score of the scale is 3. If the score is <3, it means that the job satisfaction is low. The Cronbach's alpha values for the present study were found to be 0.86 for internal satisfaction, 0.81 for external satisfaction, and 0.89 for general satisfaction.

In the evaluation of the factors affecting job satisfaction, the phenomenological (case study) method of the qualitative research was used, and the data were collected in a written form using the semi-structured questionnaire formed by the researcher. These are the following questions in the semi-structured questionnaire: "What are the positive factors that affect your job satisfaction?," "What are the negative factors that affect your job satisfaction?," and "What should be done in your workplace so that your job satisfaction will be higher than it is now?." Descriptive analysis and content analysis techniques were used in the analysis of the data, and in accordance with the original, the expressions used by the participants were included.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics, version 21.0 (SPSS IBM Corp., Armonk, NY, USA). A p value <0.05 was accepted as statistically significant.

Shapiro–Wilk test was used to determine the normal distribution of the variables, and median (min, max) was used for descriptive statistics. Categorical variables were expressed as number (n) and percentage (%).

Mann–Whitney U test was used to compare the scale scores of the two independent groups, and Kruskal–Wallis test was used in more than two groups. When there was a significant difference in the Kruskal–Wallis test, the paired comparison results (Dunn's multiple comparison test) were given.

RESULTS

In our study group, 63% of the participants were females. The mean age of the participants was 31±6.3 years, and 62% were between aged 26 and 35 years. Of the 781 participants, 71% had a bachelor's degree, 75% were married, and 92% had a monthly income of >3000 Turkish Liras. While the mean experience of the participants in the EMS field was 7.5±4.5 years, it was 10±5.8 years for all health services (Table 1).

The internal, external, and general satisfaction levels were 3.4±0.6, 2.9±0.7, and 3.2±0.6, respectively (Table 2).

When the external and general satisfaction scales are considered, there was a statistically significant difference with respect to gender variable only. Both the external and general satisfaction scale scores were significantly higher in males (Z=2.189, p=0.029 and Z=2.073, p=0.038, respectively) (Table 3).

TABLE 1. Comparison of frequencies and scale scores of socio-demographic characteristics

	n	f
Age		
18–25 years	175	23%
26–35 years	484	62%
36–45 years	89	11%
46–55 years	33	4%
Gender		
Female	495	63%
Male	286	37%
Educational status		
High school graduate	228	29%
Bachelor's degree	553	71%
Marital status		
Married	586	75%
Single	152	20%
Others	43	5%
Having children		
Yes	520	67%
No	261	33%
Income status		
<3000 Turkish Liras	64	8%
≥3000 Turkish Liras	717	92%
Profession		
Physician	28	4%
Nurse	134	17%
Emergency medical technician	434	56%
Paramedic	185	24%
Years of seniority		
0–9 years	391	50%
10–19 years	328	42%
20+ years	62	8%
Years of seniority in department		
0–9 years	539	69%
10–19 years	219	28%
20+ years	23	3%

TABLE 2. Total scores of the participants

		Scale scores		
Participants		**Internal satisfaction**	**External satisfaction**	**General satisfaction**
Total	Median (min–max)	3.5 (1–5)	3 (1–5)	3.2 (1–5)
n=781 (100%)	Mean ± SD	3.4±0.6	2.9±0.7	3.2±0.6

In Table 4, the opinions of 14 participants on factors affecting job satisfaction were grouped under four categories. The answers of the participants according to the in-depth analysis were presented below. These data were obtained from the written opinions of the participants (Table 4).

TABLE 3. Comparison of frequencies and scale scores of socio-demographic characteristics

	Internal satisfaction	External satisfaction	General satisfaction
Variables	**Median (min, max)**	**Median (min, max)**	**Median (min, max)**
Age			
18–25 years	3.67 (1, 5)	3 (1, 5)	3.3 (1, 5)
26–35 years	3.58 (1, 5)	3 (1, 5)	3.25 (1, 5)
36–45 years	3.5 (1, 4.92)	3.13 (1, 4.63)	3.3 (1, 4.8)
46–55 years	3.75 (1.33, 4.75)	3.5 (1.5, 4.75)	3.55 (1.4, 4.75)
χ^2, p	2.459, 0.483	4.225, 0.238	3.997, 0.262
Gender			
Female	3.58 (1, 5)	3 (1, 5)	3.25 (1, 5)
Male	3.67 (1, 5)	3 (1, 5)	3.35 (1, 5)
Z, p	1.524, 0.127	2.189, 0.029	2.073, 0.038
Educational status			
High school graduate	3.58 (1, 4.75)	3 (1, 4.75)	3.35 (1, 4.65)
Bachelor's degree	3.58 (1, 5)	3 (1, 5)	3.25 (1, 5)
Z, p	0.655, 0.512	0.744, 0.457	0.935, 0.350
Marital status			
Married	3.58 (1, 5)	3 (1, 5)	3.3 (1, 5)
Single	3.5 (1, 4.92)	3 (1, 4.5)	3.2 (1, 4.75)
Others	3.5 (1, 4.58)	3.13 (1, 4.25)	3.45 (1, 4.45)
χ^2, p	3.231, 0.199	3.699, 0.157	4.429, 0.109
Having children			
Yes	3.58 (1, 5)	3 (1, 5)	3.3 (1, 5)
No	3.5 (1, 5)	3 (1, 5)	3.26 (1, 4.8)
Z, p	1.679, 0.093	1.347, 0.178	1.532, 0.125
Income status			
<3000 Turkish Liras	3.75 (1, 4.58)	3.06 (1, 4.38)	3.4 (1, 4.5)
≥3000 Turkish Liras	3.58 (1, 5)	3 (1, 5)	3.3 (1, 5)
Z, p	1.650, 0.099	0.097, 0.923	0.935, 0.350
Profession			
Physician	3.65 (2.67, 4.33)	3.06 (1.5, 4.25)	3.35 (2.4, 4)
Nurse	3.67 (1, 4.92)	3 (1, 4.63)	3.38 (1, 4.8)
Emergency medical technician	3.58 (1, 5)	3 (1, 5)	3.28 (1, 5)
Paramedic	3.58 (1.08, 4.83)	3 (1, 5)	3.25 (1.05, 4.8)
χ^2, p	2.619, 0.454	1.114, 0.774	2.172, 0.537
Years of seniority			
0–9 years	3.61 (1, 5)	3 (1, 5)	3.3 (1, 5)
10–19 years	3.5 (1, 5)	3 (1, 5)	3.25 (1, 5)
20+ years	3.58 (1.33, 4.92)	3.25 (1.5, 4.75)	3.45 (1.4, 4.8)
χ^2, p	1.648, 0.439	4.987, 0.083	4.321, 0.115
Years of seniority in department			
0–9 years	3.58 (1, 5)	3 (1, 5)	3.3 (1, 5)
10–19 years	3.58 (1.92, 5)	3 (1, 5)	3.25 (1.85, 5)
20+ years	3.5 (1.33, 4.33)	3 (1.5, 4.38)	3.3 (1.4, 4.15)
χ^2, p	0.004, 0.998	0.860, 0.651	0.521, 0.771

TABLE 4. Opinions of the participants on the factors affecting job satisfaction

	Positive factors	Negative factors	Factors increasing the satisfaction
Physical causes		Poor physical conditions of ambulance stations. Uniforms are non-ergonomic and not in the correct color. Design of ambulances. Difficulties in transportation to the work.	Improvement of physical conditions in stations and ambulances. Easy transportation to work. Ergonomic uniforms.
External causes	Being appreciated by directors. When patients or their relatives are grateful to the employees.	Inability to access directors. Not taking into consideration the recommendations of employees by directors. Employees are not given the right to make their own decisions. Not being appreciated. Absence of career opportunities. Scientific studies are not supported. Intensive work. Lack of personnel number. Low wages. Unpaid premiums and unfair distribution of premiums. Serving non-emergent cases. Lack of safety measures. Exposure to physical and verbal violence. Prejudiced behaviors of hospital emergency department professionals.	Being appreciated by directors and patients. Career opportunities. A fair wage system based on the level of education, performance, and career. Serving only emergent cases. Professional development and career opportunities. Providing security measures. Providing measures related to violence. Reduction in prejudices.
Internal causes	Saving lives of patients. Successful interventions. Employees are proud of their work. Employees' loving his/her profession. Feeling special because of his/her profession.	Failure of intervention.	Achieving success by increasing the level of vocational education. Ensuring personal development.
Social causes	Good image of the profession in society. Teamwork. Strong communication.	Lack of social support systems. Bad communication in the team.	Providing social issues. Strengthening the communication within the team and related institutions. Arrangement of art and sports activities.

The opinions of the participants on physical causes were as follows:

Participant 1. "The emergency aid bag is too heavy and not user friendly."

Participant 8. "Clothes, especially trousers and coats, can be made of softer and quality fabric (in terms of easier intervention)."

The opinions of the participants on the external causes were as follows:

Participant 9. "It is necessary to take preventive measures on verbal and physical violence against health professionals, and increase the rates of penalties."

Participant 10. "There are no career opportunities. There is no rank or wage classification according to the level of education."

Participant 14. "Safer workplace, and prevention of violence... My dreams."

The opinions of the participants on the internal causes were as follows:

Participant 10. "To be aware of what I can do in every case; to influence people's lives... It gives me satisfaction. I feel like I'm special when I put on my uniform and got on the ambulance."

Participant 13. "Because I love my job. It is not possible to get satisfaction from any job that you do not love."

The opinions of the participants on the social causes were as follows:

Participant 5. "Arrogant team mates; Persons who are trying to get rid of work; Executives who cannot make empathy... Lack of social support systems at work."

Participant 10. "The society is prejudiced against my work, and they criticize my work even though they know nothing about it."

DISCUSSION

In the present study, it was found that the general and internal job satisfaction of the employees in EMS was moderate, whereas their external job satisfaction was low.

The majority of the participants were females and young. In a study conducted by Duran et al. (17) in the EMS field, it was observed that female and young employees were in the majority. The employees stated that they were generally satisfied with their work, but the security measures were insufficient.

In another study by Atan et al. (5), gender, marital status, having children, seniority years, and education level variables were not found to be correlated with job satisfaction. According to the study conducted by Tarcan et al. (14), gender, age, education, and marital status variables had no significant effect on any form of

satisfaction. In our study, external satisfaction and general satisfaction rates of female employees are lower than those of male employees. This is thought to be due to the fact that females are more sensitive, deal with housework and childcare, and working in pre-hospital EMS requires intense physical force.

When the opinions of the participants are examined, it is seen that they mostly have positive considerations on internal causes. In accordance with the structure and aim of the pre-hospital EMS, the successful interventions of the employees to save lives can be considered as one of the most important factors that enable them to be satisfied by their jobs. The factors negatively affecting employees' job satisfaction are generally external factors. Wage distribution, education level, career opportunities, security measures, prevention of violence, managerial problems, and non-emergent cases are important issues in this field.

The participants also mentioned that the ergonomics of their uniforms and of emergency aid bags were factors affecting their job satisfaction. There are no studies in the literature on this subject. However, considering that EMS is a work that requires constant and rapid movement, the ergonomics of uniforms and bags can significantly affect the operation of the work. New studies should be conducted on this issue.

In the study conducted by Khatiban et al. (18), the participants generally perceived participation in managerial decisions related to their work as inadequate, and they considered this as an obstacle to job satisfaction. They also stated that the quality of existing equipment and materials, planning of work shifts, lack of coordination between personnel, and verbal and physical violence are factors that negatively affect job satisfaction. In the study conducted by Andel et al. (19), it was found that low job satisfaction was reflected on the performance of the employees, and that this reflection caused verbal violence when noticed by the patients and their relatives. In other words, violence decreases job satisfaction, and decreasing job satisfaction causes violence again.

In pre-hospital EMS, the working environment is often seen as unsafe environments by employees. In the study by Ujevic et al. (2), it was found that employees working at the ambulance had lower job satisfaction than those working in the call center or in the office of the EMS. The findings of the present study are similar to those in the literature.

The present study is limited to the city where the study was conducted. EMS employees in other cities may have different results. Since the literature on the EMS field is insufficient, no clear comparison could be made.

The external satisfaction level of EMS professionals is low. Problems related to access to management, participation in management, career opportunities, wages, security, being appreciated, and prevention of violence negatively affect job satisfaction. It may not be possible to eliminate these issues completely, but improvements are recommended. Different factors, such as appreciation, rewarding, personal accomplishment, merit, and social opportunities, that positively affect job satisfaction should be supported and increased.

Ethics Committee Approval: Ethics committee approval was received for this study from Ankara Yıldırım Beyazıt University (Approval Date: 18/09/2018, Approval Number: 41).

Informed Consent: Written informed consent was obtained from the individuals who accepted to participate in the study.

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Women's Experience of Cesarean Section: A Qualitative Study

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BACKGROUND/AIMS
Having a positive or negative experience of labor affects the method of delivery women select for their next pregnancy. Having a positive experience also helps women feel in control, thus improving the relationship between them and their babies and the quality of care they are able to provide. Therefore, the aim of the present study was to understand women's experiences of having a C-section and to determine their feelings and thoughts on this subject in the early postpartum period.

MATERIAL and METHODS
This was a qualitative descriptive design study. A total of 27 women who had given birth by C-section in the obstetrics and gynecology clinic of a university hospital between November 2016 and February 2017 were included in the study. Data were collected using a questionnaire form for socio-demographic information and a semi-structured interview that discussed the women's experience of C-section. Data were analyzed using the content analysis method.

RESULTS
Five categories were identified with regard to women's experiences of C-section. These were "their knowledge about C-sections," "their feelings about the decision to give birth by C-section," "their feelings immediately before delivery," "their experiences after the C-section," and "their opinions on the effects of the C-section on their relationships with their babies."

CONCLUSION
The women viewed a C-section as a surgical intervention. They experienced fear and anxiety when going into the operating theater and suffered mostly from afterpains. Healthcare professionals should be aware of women's experiences and should develop practices that allow them to express their thoughts and feelings about cesarean birth.

Keywords: Cesarean birth, C-section, women's experience, qualitative study

INTRODUCTION

A cesarean section is a surgical procedure for the removal of the fetus by cutting into the abdominal wall and then the uterus. If it is thought that either the mother or the baby may not survive after a vaginal delivery, or if both of their lives are in danger, then a C-section is vital (1). The World Health Organization has suggested that C-sections should occur in between 5% and 15% of all births (2). However, the cesarean rate in Turkey is much higher than this. The percentage of cesarean births, which was 21% in 2002, increased to 51% in 2014 and then to 53% in 2015 and 2016 according to data from the Turkish Ministry of Health (3).

In recent years, women have had a high number of C-sections both for medical reasons and as a result of demands for a cesarean delivery in the absence of any medical reason (4). Pregnant women decide to give birth by C-section because of their uncertainty about being in labor, worry about the pain and suffering they will experience, fear that their labor will be unsuccessful, concern about giving birth without any trusted health personnel present, and as a result of the influence of their social environment (5). In fact, as a surgical intervention, a C-section is not necessarily easy or pleas-

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ant because of the pain that it causes, the lack of control during delivery, the length of the healing process, and the delay that may be experienced in establishing the mother–infant relationship. Women who have cesarean deliveries experience anxiety about the risks of the operation and have fears about the long period of recovery and pain after a C-section compared with a vaginal delivery (6). Amanak and Karaçam found in their study with 235 women who gave birth by C-section that women experience problems related to pain in the workplace and difficulties in moving, passing wind, feeding, and producing stools during the postpartum period. Their study determined that women had problems related to feeding their babies, cleaning themselves, and dressing and caring for their stomachs (7). It was determined that even when the C-sections had been planned, the women were not happy about the afterpains and fear that they had experienced (8). In addition, the positive or negative experiences women have during childbirth influence the method of delivery they select for their next labor (9).

An unplanned and emergency C-section, the type of anesthesia used in a cesarean section, and their perceptions and experience of labor all affect the satisfaction women derive from giving birth. A positive experience of labor helps women to feel more in control, therefore improving their relationship with their babies and the quality of care they are able to provide. Thus, it is important to understand the experiences of women in the early postpartum period and to determine their feelings, thoughts, and experiences about giving birth. Women's perceptions of their C-section, how they understand it, how they respond to it, what feelings they experience most after childbirth, the difficulties they encounter, and how they deal with these difficulties all affect the postpartum care of the mother and baby. Being aware of these will enable health professionals who provide primary care to feel more in control and help them to decide on and offer the best care. Thus, the aim of the present study was to investigate the experiences of women in the early postpartum period and to determine their feelings, thoughts, and experiences about giving birth via C-section.

MATERIALS and METHODS

The research was conducted using a phenomenological approach, which is a qualitative research method. In the phenomenological approach, the researcher is interested in how the participants perceive the events they are experiencing and how participants attribute a meaning to them through their own descriptions.

The study was approved by the Near East University ethics committee (approval date: 20/10/2016, approval no.: 327). There is no specific sample number in qualitative studies, and the present study used the purposive sampling method. The population of the study consisted of women undergoing C-sections at the obstetrics and gynecology clinic of a university hospital between November 2016 and February 2017. The study sample included 27 Turkish-speaking women who underwent C-sections between the dates specified and who agreed to participate in the study. Participants were informed in writing and orally about the aim of the study, its confidential nature, its voluntary basis, and their right to end the interviews whenever they wished. Informed consent was obtained from the women who participated in the study.

Data were collected using a form with 15 questions about the socio-demographic characteristics of the women and 10 semi-structured interviews, including questions about the women's knowledge about cesarean birth, their thoughts after a cesarean birth had been decided on, and their experience after their C-sections (post-cesarean delusions).

The researcher conducted individual in-depth interviews in the women's rooms in the first 48 h after delivery. During the interviews, the researcher ensured that the women were not suffering from any severe pain and had finished breastfeeding their newborns. As the babies were sleeping after breastfeeding, the mothers were comfortable, and this ensured that they were able to answer as they wished.

During the interview, the participants were observed by the interviewer, and their behaviors and moods were noted along with their statements. The interviews lasted for 20–25 min and were recorded with the participants' consent.

In addition, the researcher asked the participants to listen to the audio recordings after the interviews, and their consent to proceed was received. They were also asked whether they had anything else they wished to say.

Statistical Analysis

All audio recordings were transferred to the computer by the researcher on the same day. The participants' statements were transcribed and read individually by the researchers, and content analysis was used to determine what the statements meant and how categories could be formed from them.

The analysis of the data generated five categories (no computer-assisted qualitative data analysis software was used). To test the validity of the study, the data obtained from the interviews were examined by two faculty members who were experienced in qualitative research, and the consistency of the researchers was checked.

RESULTS

The study was conducted on 27 women who agreed to participate. The mean age of the women was 31.3±7.2 years. Of the 27 women, 66.6% were university graduates, and 51.8% were employed. Among them, 51.8% had just had their first gestation, and the interbirth intervals of 75% of the women who had become pregnant twice or more were ≥3 years. Of the 27 women, 96.2% had had to give birth by cesarean delivery for medical reasons, and 70.3% stated that they would not have selected a C-section if there were no medical reasons to do so. Among them, 85.1% had delivered by a C-section under epidural anesthesia.

Five categories emerged as a result of the qualitative analysis of the interviews. These were "their knowledge of C-section," "their feelings about the decision to give birth by C-section," "their feelings immediately before delivery," "their experiences after the C-section," and "their opinions on the effects of the C-section on their relationships with their babies."

Category I: their knowledge of C-section

Most of the women stated that they heard something about C-sections, but they had not researched it and did not have

detailed information. Most of them knew the C-section was an operation and had knowledge of the forms of anesthesia used:

"I'd picked up some knowledge about C-sections. General or epidural anesthesia is administered; I did not know anything except this. My view about it is positive; it is one of the best medical choices. People who'd given birth by C-section were generally satisfied, they recommended it." (Mother 8).

"I didn't know anything about C-sections. I'd heard that a C-section is like surgery, so it's hard and the mother gets scars." (Mother 12).

"The only thing I know about the C-section is that if a woman has previously had one, she can only give birth by cesarean in any future pregnancies."

Women who had had their first delivery by C-section had some knowledge of it:

"I knew about having a C-section. It is more difficult to recover after wards. It was just like that in my first labor." (Mother 9).

"I knew about it. I had a C-section during my first labor, so, for instance, I knew it was hard to pass wind. I knew that if you give birth by C-section in your first labor, you have to give birth by a C-section the next time." (Mother 26).

Category 2: their feelings about the decision to give birth by C-section

Women who gave birth by cesarean delivery after having expected to give birth by vaginal delivery stated that they experienced sadness and worry:

"I was disappointed when I heard that I was giving birth by C-section because I was focused on a normal delivery. I thought a normal delivery would be better for me and the baby." (Mother 1).

"I felt very bad when a C-section was decided on. I was worried. If it wasn't absolutely necessary I would have insisted on a normal delivery, but I gave birth by C-section because my baby defecated." (Mother 18).

"I didn't know anything about a C-section. It was decided on at the 35th week. I don't think that's good; it would have been better if it had been normal delivery; I was sad." (Mother 25).

Some of the women stated that they gave birth by C-section but would have preferred to have had normal delivery:

"A C-section is good when it's necessary, but there should be a normal delivery when there's no problem." (Mother 17).

"It shouldn't be done when it's not compulsory, because normal birth is natural and adapting to it is easier. The body recovers more quickly. You have to have an incision and you're anesthetized when you give birth by C-section." (Mother 24).

Category 3: their feelings immediately before delivery

Most of the women stated that they worried because C-section is a surgical operation performed under anesthesia:

"I was afraid. I thought, 'I am going to have an operation under anesthesia, will this affect my baby?' But nothing happened. You have to be brave to undergo an operation." (Mother 2).

"When I underwent a C-section, I felt a bit anxious, a bit frightened. I kept wondering, 'Will something go wrong? Will I be in pain?'" (Mother 13).

One woman stated that she did not think she was going to be frightened because she was giving birth by C-section for the second time, but she worried about her previous surgery site when she underwent her C-section:

"I had a C-section for my first delivery, so I thought that they'd cut the same area. I thought this would be a difficult experience." (Mother 26).

Most of the women who planned to give birth by C-section were excited about seeing their children and curious about the health of their babies and how they would react:

"I was excited to have a C-section, because I had carried my baby and I became emotional and cried when I saw my baby." (Mother 7).

"It's a very nice feeling. I experienced it like a normal birth. I dreamed about my baby before giving birth. I wish everything was this beautiful." (Mother 19).

"I felt excitement and fear, I prayed that both of us would just be well. I felt it when I underwent the operation. I was excited. I was glad to see the baby." (Mother 22).

The women who underwent a cesarean section without planning stated that they were worried about their health and had mixed feelings:

"When the doctor told me I would be having a cesarean, my only thought was to get rid of my pain. It did not matter if it was a C-section or normal delivery. But I was scared again." (Mother 14).

"It was a last-minute decision. When my waters broke suddenly, they gave me a cesarean. I was scared when I went into the operating theater. I thought the baby would be thirsty, so I was very worried." (Mother 18).

"Having the C-section was very different. It was sad because I expected to give birth normally but I gave birth by cesarean. It was also happy because of the thought that I would meet my baby in an hour. I had mixed feelings." (Mother 19).

One woman stated that she was sad that her baby would no longer be part of her after she had her C-section:

"When I was going to give birth, I was sad because my daughter would leave my body and we would be separated. I had got used to feeling my baby inside me, and I thought that they would separate us when I gave birth." (Mother 15).

Category 4: their experiences after the C-section

The women stated that they were most likely to experience abdominal pain after the C-section:

"I was in pain after the operation, I didn't sleep well and I was uncomfortable when I couldn't lactate. I would have liked to be able to feed immediately." (Mother 6).

"The pain was too much after the C-section. It was more than I expected. I had difficulty breathing. I don't feel sorry about giving birth by cesarean, I'm just in pain." (Mother 20).

Most of them stated that they were sad because they could not breastfeed their babies due to the distress and pain they experienced after the C-section:

"Afterwards, I felt pain and regretted having it because I had a lot of pain. It was hard not to be able to walk or to stand up and to have to deal with coughing. I was afraid because the C-section was my first operation. I was worried about the surgical incision." (Mother 1).

"It's not like a normal birth, lactation is generally late. I tried to lactate this morning. I would probably have been able to lactate earlier, if I hadn't given birth by C-section." (Mother 12).

Category 5: their opinions on the effects of the C-section on their relationships with their babies

Most of the women stated that they had difficulty breastfeeding and holding their babies because of the pain:

"I didn't hug my baby straight away, but I don't think that the bond between me and my baby was affected, because I had already carried my baby for nine months, so a bond had already been established." (Mother 1).

"I think that a normal delivery might have been better for my relationship with my baby, because I had a lot of pain. But I felt better saying 'It had to be like this.'" (Mother 21).

Women who gave birth under epidural or spinal anesthesia stated that they had no problem with their babies because they were able to see them immediately:

"Even though I gave birth by C-section, I experienced the moment my child was born. I was lucky I was not under general anesthesia. I never thought 'I wish I would given birth by normal delivery.'" (Mother 6).

"I chose to have an epidural so I could see my baby. I saw everything. I was relaxed, I saw and kissed my baby." (Mother 10).

"Actually, I saw my baby straight after birth because I had an epidural. They brought my baby straight to my bed. In my eyes, there's no difference between the two of them." (Mother 19).

Some women stated that they thought that their relationship with their baby would have been better if they had given birth normally:

"There is a difference between a C-section and normal delivery: you feel labor pains in normal delivery, the mother feels more during the birth. The bond with the child is strong because you're awake during the whole process, from the beginning to the end, when you give birth normally." (Mother 5).

"There's a difference between a C-section and normal delivery. Lactation is late after a C-section but lactation occurs immediately after normal delivery. I couldn't breastfeed my baby; this might have affected our relationship at the start." (Mother 8).

DISCUSSION

How their baby will be delivered is an important issue for pregnant women. From the point at which women begin to plan to become pregnant, they also start to be concerned about the delivery method (10). It is very important to ensure that pregnant women have adequate information and counseling from health professionals so they can decide on the most appropriate form of delivery. Being informed about the delivery methods reduces women's anxiety, whether they given birth via a vaginal or cesarean delivery (11). The women who participated in our study stated that they had heard a lot about C-sections but had not tried to find out more. The reason for this may be that most of the women who participated in the present study gave birth by C-section on the advice of their doctors. According to the literature, pregnant women generally obtain information about C-sections from their doctors, whereas their information about vaginal delivery comes from midwives. It is important that doctors, nurses, and other health professionals help pregnant women to have a positive experience of giving birth and ensure that they are able to actively participate through planned health education, psychoeducation, and similar psychosocial interventions (12).

Women's perceptions of childbirth are influenced by their personal characteristics, their expectations, and their experiences of previous deliveries (13). In this regard, it was found that women who had delivered their first child by C-section were more experienced and therefore had more knowledge about cesarean birth. Most women described a C-section as an operation. Normal delivery is a natural physiological process. A C-section is not an alternative to normal delivery but a surgical procedure that should only be performed when there is a problem with normal childbirth. In the present study, the women's definition of a C-section as a surgical procedure supports the finding that most of them would have selected normal delivery if they had been able to. However, some of the women stated that "If the first birth was by C-section, subsequent births have to be by C-section." Nonetheless, studies have emphasized that individuals who have previously had C-sections are able to deliver vaginally during subsequent labors and should be encouraged to give birth by vaginal delivery (14, 15). Vaginal birth after cesarean (VBAC) is recommended only after appropriate information and consultation have been provided and when the situation meets the required conditions as stated in the Management Guidelines on Birth and Cesarean Delivery as published by the Turkish Ministry of Health (16). Kavak et al. (17) observed only one case of uterine rupture in 68 women having VBAC in their retrospective study. One study analyzed the level of knowledge of health professionals about this subject and the proportion of health professionals who stated that women who have delivered by C-section may be able to give birth normally in subsequent labors was found to be 72.7% (18). Given that not all health professionals have accurate knowledge of the topic, it may not be appropriate to expect a full understanding of the subject in participants who are not health professionals. Nevertheless, the lack of knowledge of this subject among the pregnant women

in our study shows that it is important that nurses, doctors, and other health professionals provide pregnant women with up-to-date information while they are preparing to give birth, so that they can make the right decision at the right stage of the process.

The present study found that the women who gave birth by cesarean delivery after expecting to give birth normally experienced fear, sadness, and anxiety. The perinatal period is an important period in which women prepare themselves for labor; women generally decide how they will give birth in this period. Currently, women want to have a say about the delivery method and to participate in the decision-making process. Any woman who has to decide on the delivery method will be influenced by her own style of decision-making. At this stage, physicians and nurses have a responsibility to ensure that the woman participates fully in making the decision while also encouraging her to decide on the appropriate delivery method and providing clear and accurate information (19). Nurses in particular should help pregnant women to deal with any anxiety and to think about what the healthiest delivery method may be. In pregnancies in which a C-section had suddenly become necessary for medical reasons, the mothers were found to be concerned about their babies' lives and to have concerns about the operation. In particular, women who were giving birth by cesarean delivery for the first time experienced these feelings more intensely. Studies in the literature on the psychological problems experienced by pregnant women about both normal delivery and C-sections support our findings. Pregnant women who give birth by C-section experience fear about being paralyzed and are frightened that they will not come round after being anesthetized or that they will bleed out. A sudden decision to perform a C-section may increase the psychological problems experienced by pregnant women according to both our results and the literature (20, 21).

In the present study, the mothers experienced positive feelings, such as astonishment, getting emotional, crying, excitement, and happiness, when they first met their babies. Mothers can maintain a happy, peaceful, and healthy mother–infant relationship when they are ready for motherhood and when their pregnancy has been planned. The participants in our study had infants with no health problems and this might have helped them to have positive feelings and have made it easier for healthy mother–infant communication to begin.

In the present study, the participants' most common problems were found to be negative experiences, such as pain in the site of sutures, difficulties with movements, difficulty in performing daily life activities, especially infant care, and late lactation. Negative experiences after a C-section may make it difficult for women to adapt to the role of being a mother, develop a bond with the baby, or demonstrate healthy mothering behaviors (22).

Nurses have the very important responsibility of managing women's pain after childbirth, using methods including pharmacological interventions (23). Mothers may be worried about motherhood and caring for their infant as a result of the pain they are experiencing. Therefore, it is important that nurses both inform mothers about what to expect in the postpartum period and provide advice to mothers when they need it. Studies have shown that mothers who give birth by C-section are more likely to need the support of health professionals to interact with their babies during the first days of life than mothers who give birth by normal delivery (24).

Some of the women who gave birth by C-section stated that if they had given birth by normal delivery, they would have had a better relationship with their babies after delivery, and that lactation might have occurred earlier. Studies have shown that mothers who deliver by C-section cannot communicate properly in the early postpartum period because of their pain, the limitations to their movement, and late lactation. The process of giving birth may be defined as a trauma for mothers who cannot immediately hug and breastfeed their baby due to the pain they are experiencing (25, 26). Our findings suggest that normal birth is a more appropriate method for establishing a healthy mother–infant relationship in early life. The support of nurses, doctors, and other health professionals is important for establishing strong bonds between infants and mothers in the postpartum period whether there has been a normal delivery or a C-section (27). After a C-section, mothers cannot comfortably hug their babies, and establishing a safe mother–infant relationship may be delayed because of pain at the surgical site, restrictions on movement, feelings of weakness, and an inability to get up, as seen in our results (28).

In conclusion, it was determined that women preferred vaginal delivery to a C-section, considered a C-section to be a surgical intervention, experienced fear and anxiety when going into the operating theater, and suffered mostly from afterpains. Health professionals should ensure that the women who have a C-section are relaxed and comfortable when they are preparing them physically for the procedure. Women should be able to express their feelings, and therapeutic communication techniques should be used to inform them about the operation they will undergo and to listen to their responses. It is important, both for the postpartum mother–infant relationship and for planning healthcare, that women know about these experiences and that practices are developed that allow them to express their thoughts about childbirth. Further studies on how to develop these practices are recommended. Qualitative studies should also be conducted to investigate the experiences of cesarean among women with different cultural and social backgrounds.

The present study has limitations. As this research is a qualitative study, the results are limited to the study group and cannot be generalized to all women. In addition, the present study was performed with a small sample size and in one hospital; thus, the possibility of transferring these findings to other populations is limited.

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

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The Evaluation Factors Affecting Sleep Quality and Depression Levels in Chronic Hepatitis B and C and Liver Cirrhosis

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BACKGROUND/AIMS
Physical and mental symptoms, such as sleep disturbances and depression, are common problems in patients with chronic hepatitis B and C (CH-B and CH-C) and liver cirrhosis (LC). Poor sleep and depression negatively impact patients' quality of life and cognitive functions. The objective of the present study was to search the affecting factors of sleep quality and depression levels in patients with CH-B, CH-C, and LC.

MATERIAL and METHODS
We performed a descriptive and cross-sectional study of 135 patients with CH-B and CH-C and 75 patients with LC in two training hospitals. Data were gathered by application of an introductory form, Pittsburgh Sleep Quality Index, and Beck Depression Scale to 135 patients with CH-B and CH-C and 75 patients with LC. Percentage, t-test, one way analysis of variance, Tukey test, and Pearson correlation analysis were used for statistical analysis.

RESULTS
It is found that patients' sleep qualities are meaningfully worse in the hepatitis patient groups that are between 51 and 74 years, female patients who do not have a job and taking antidepressant medicines, patients who have hypertension and taking antihypertension medicines, and patients who have chronic lung diseases and the cirrhosis patient groups that have been treated for a long time than in the other groups. A positive relationship was detected between sleep quality and depression levels in CH-B, CH-C, and LC.

CONCLUSION
In patients with CH-B, CH-C, and LC, poor sleep quality is strongly related to depression. We suggest that the evaluation and treatment of sleep disturbance to assess patients could improve the quality of life.

Keywords: Cirrhosis, hepatitis B, hepatitis C, dleep quality, depression

INTRODUCTION

Chronic hepatitis B and C (CH-B and CH-C) infection currently is one of the most important health issues worldwide (1). Liver cirrhosis (LC) is a consequence of chronic liver disease most commonly caused by alcoholism, viral hepatitis, autoimmune disorders, or other etiologies. Patients with cirrhosis are exposed to many complications to develop, and thus the average life expectancy decreases significantly. For patients with LC, life becomes meaningless due to symptom-related physical and psychological problems. The incidence rate of negative emotions in patients with chronic hepatitis has been reported to be 38.1%–51.1%, among which 47% of patients have anxiety problems and 68% of patients have mild-to-moderate depression (2, 3).

Regular sleep routine is an important health variable that may affect the quality of life and wellness of the individual. Sleep routine has so many positive effects for human life; however, disturbed sleep affects the individuals negatively and causes problems, such as difficulties in focusing, anxiety, depression, increase in sensitivity to pain, irritability, hallucinations, anorexia, and difficult urination (4, 5). Several sleep disturbances have been described in cirrhosis. In chronic diseases, such as CH-B, CH-C, and LC, sleep disturbances, such as difficulty with falling asleep, fragmented nighttime

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sleep, and increased daytime somnolence deterioration in the sleep–wakefulness cycle, may be seen. The patients usually are sleepy during the days and agitated or have difficulties to fall asleep. In some patients, the sleep–wakefulness cycle may even become reversed (6). At the same time, patients with end-stage liver disease have committed suicide because of depression. In our literature search, which we made in our country, we did not find many studies about sleep quality and depression in patients with CH-B, CH-C, and LC. The aim of the present study was to examine (1) what are the sociodemographic factors affecting sleep quality in patients with CH-B, CH-C, and LC?, (2) what are the associated with the disease affecting sleep quality in patients with CH-B, CH-C, and LC?, and (3) what are the sleep quality and depression levels in patients with CH-B, CH-C, and LC?.

MATERIAL and METHODS

The descriptive and cross-sectional study was conducted on adults diagnosed for at least 6 months, 135 patients with CH-B and CH-C and 75 patients with LC who voluntarily accepted to participate in the study in two training hospitals with ethical committee confirmation received from the Provincial Directorate of Health of Istanbul. Before the data collection, a written informed consent was also obtained, and the researchers explained the study aims. Data from the patients were obtained upon filling out three forms: introductory information form, Pittsburgh Sleep Quality Index (PSQI), and Beck Depression Scale (BDS). The introductory information form includes sociodemographic variables (age, sex, marital status, educational status, and working status) and disease variables (duration of treatment, used drugs, and additional diseases).

Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index is a scale employed to determine the sleep quality of the last month and was developed by Buysse et al. (7). The scale consists of 19 questions, and the evaluation of sleep quality is scored as 0 for very good, 1 for good enough, 2 for bad enough, and 3 for very bad. The global score obtained in the questionnaire ranges between 0 and 21, and high values indicate bad sleep quality and high sleep disorder level. A global score of 5 indicates a significantly bad sleep quality clinically. The scale was adapted for Turkish patients by Agargun et al. (8).

Beck Depression Scale

The original form of the scale was prepared by Beck et al. (9). BDS was translated into Turkish, and valid confidence studies have been performed. In the present study, the 1978 version, adapted by Hisli (10), has been used. In the form of BDS, there are four choices for each of 21 symptom categories. Each item may have points between 0 and 3. The highest score that may be obtained is 63. High total score indicates depression in high level or severity. In our study, Cronbach's alpha coefficient of the scale was read as 0.801 for patients with hepatitis and 0.804 for patients with cirrhosis.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences program version 15 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (number, percentage, average score, and standard deviation), t-test, one way variance analysis, Tukey test, and Pearson correlation analysis were used in the statistical analysis of data. Internal consistency was examined through Cronbach's alpha test evaluation. A p value <0.05 was considered significant.

RESULTS

The average age of patients with CH-B and CH-C included in the study was 45.53±13.69 years, and 70 (51.9%) were females. The average age of patients with LC was 55.64±11.51 years, and 29 (38.7%) were females.

It was seen that PSQI scores were higher in the 51–74 age group in patients with CH-B and CH-C than in the 19–35 age group ($p<0.05$). PSQI scores were higher in female patients than in male patients ($p<0.05$). It was revealed that unemployed patients had higher score than working people ($p\leq0.01$). There was no statistically significant difference between marital status and total PSQI score ($p>0.05$) (Table 1).

TABLE 1. Average scores of sociodemographic variables according to PSQI scale in patients with LC

Variable	Variable	N	%	Average score±SD	Test values
Age (year)	19–35	38	28.1	3.81±2.16	F=3.80
	36–50	43	31.9	5.34±3.67	p=0.02*
	51–74	54	40	5.55±3.26	
Sex	Female	70	51.9	5.54±3.63	t=2.06
	Male	65	48.1	4.41±2.58	p=0.04*
Marital status	Married	110	81.5	4.80±2.99	t=1.52
	Single	25	18.5	5.88±3.98	p=0.12
Working status	Employed	40	29.6	4.0±2.49	t=2.39
	Unemployed	95	70.4	5.42±3.39	p=0.01**
Educational status	Primary school	92	68.1	5.17±3.05	F=1.31
	High school	26	19.3	5.15±3.89	p=0.27
	Bachelor and beyond	17	12.6	3.82±2.76	

*p<0.05, **p≤0.01
SD: standard deviation

There was no statistically significant difference between total PSQI score and age groups, gender, marital status, employment status, and education in patients with LC (p>0.05) (Table 2).

Pittsburgh Sleep Quality Index scores in those who receive antihypertensive treatment were higher than those who do not (p<0.05). Patients who have hypertension (p≤0.01) and who have chronic obstructive pulmonary disease (COPD) (p≤0.05) had higher PSQI scores than those who do not have. There was no statistically significant difference between total PSQI score and variable of treatment duration in patients with CH-B and CH-C according to the Tukey test result (p>0.05). There was no statistically significant difference between total PSQI score and variables on administration of antiviral drugs (p>0.05) (Table 3).

In patients with LC, patients who received treatment since 72–396 months had higher scores than those who had treatment duration of 25–60 months according to the Tukey test result (p<0.05). In patients with LC, there was no significant difference between total PSQI scores and variables on antiviral and antihypertensive drugs administration status (p>0.05). There was no statistically significant difference between total PSQI scores and condition of having hypertension and COPD in patients with LC (p>0.05) (Table 4).

We performed Pearson correlation analysis to analyze the relationship between total PSQI score and BDS in patients with CH-B and CH-C, and we determined a weak level significant positive relationship between BDS and total PSQI score (r=0.439, p<0.01).

With respect to patients with LC, we determined a weak level significant positive relationship between BDS and total PSQI score (r=0.448, p<0.01) as a result of Pearson analysis performed to analyze total PSQI score and BDS.

We observed in our study that BDS scores of patients with CH-C were higher than those of patients with CH-B, and patients with cirrhosis had BDS scores higher than those with CH-B and CH-C (p≤0.01) (Table 5).

TABLE 2. Average scores of sociodemographic variables according to PSQI scale in patients with LC

Variable	Variable	N	%	Average score±SD	Test values
Age (year)	23–40	7	9.3	4.85±3.48	F=0.45
	41–55	31	41.3	5.32±2.82	p=0.63
	56–81	37	49.3	5.94±3.83	
Sex	Female	29	38.7	5.72±3.67	t=0.27
	Male	46	61.3	5.50±3.24	p=0.78
Marital status	Married	58	77.3	5.22±3.26	t=1.73
	Single	17	22.7	6.82±3.64	p=0.88
Working status	Employed	19	25.3	5.63±3.45	t=0.06
	Unemployed	56	74.7	5.57±3.40	p=0.94
Educational status	Primary school	50	66.7	5.80±3.61	F=0.59
	High school	13	17.3	5.0±2.64	p=0.55
	Bachelor and beyond	12	16.0	4.66±2.22	

TABLE 3. Average scores of disease variables according to PSQI scale in patients with CH-B and CH-C

Variable	Variable	N	%	Average score±SD	Test values
Treatment duration	No treatment	28	20.7	5.32±2.94	F=0.53
	1–24 months	49	36.3	4.57±2.9	p=0.66
	25–60 months	31	23.0	5.38±3.98	
	61–300 months	27	20.0	5.0±3.08	
Antiviral drugs	Not used	77	57.0	4.79±3.13	t=0.86
	Used	58	43.0	5.27±3.31	p=0.38
Antihypertensive drugs	Not used	111	82.2	4.61±2.86	t=3.11
	Used	24	17.8	6.79±4.07	p=0.02*
Hypertension	Does not exist	98	72.6	4.38±2.59	t=3.78
	Exists	37	27.4	6.62±4.05	p=0.01**
COPD	Does not exist	100	74	4.9±2.99	t=1.917
	Exists	35	26	8.0±7.65	p=0.05*

*p≤0.05, **p≤0.01
COPD: chronic obstructive pulmonary disease; SD: Standart Deviation

TABLE 4. Average scores of disease variables according to PSQI scale in patients with CH-B and CH-C

Variable	Variable	N	%	Average score±SD	Test values
Treatment duration	Not receiving treatment	4	5.3	5.50±3.31	F=2.81*
	1–24 months	37	49.3	4.89±2.45	p=0.045
	25–60 months	13	17.3	4.76±3.13	
	72–396 months	21	28.0	7.33±4.43	
Antiviral drugs	Not used	44	58.7	5.63±3.32	t=0.150
	Used	31	41.3	5.51±3.53	p=0.881
Antihypertensive drug	Not used	60	80.0	5.76±3.65	t=0.91
	Used	15	20.0	4.86±1.95	p=0.36
Hypertension	Does not exist	52	69.3	5.59±3.43	t=0.036
	Exists	23	30.7	5.56±3.38	p=0.97
COPD	Does not exist	69	92.0	5.46±3.36	t=1.06
	Exists	6	8.0	7.0±3.74	p=0.29

*p<0.05
COPD: chronic obstructive pulmonary disease, SD: Standart Deviation

TABLE 5. Comparison of PSQI and BDS scores of patients with CH-B, CH-C, and LC

Variable	Group	N	Average score±SD	Test values
BDS	Hepatitis B	107	8.24±6.16	t=9.31
	Hepatitis C	28	11.57±5.14	p=0.01**
	Cirrhosis	75	12.26±7.29	
PSQI	Hepatitis B	107	4.62±2.93	t=4.25
	Hepatitis C	28	6.42±3.83	p=0.016*
	Cirrhosis	75	5.58±3.39	

*p<0.05, **p≤0.01
BDS: Beck Depression Scale; PSQI: Pittsburgh Sleep Quality Index

DISCUSSIONS

Psychiatric disorders are frequent in patients with CH-B and CH-C (11). While anxiety, distress, and complaints cause a marked stress clinically, they also cause deterioration in social and professional fields or in fields in which functionality is important. Difficulties in focusing his thoughts in a certain subject, undecidedness, suicide thoughts, or attempts can be seen (12).

Liver cirrhosis is a disease that represents the final stage of several chronic liver diseases. Psychological stress and depression seen in LC are related to the severity of the disease (13). In our study, sleep quality was observed to be worse in the 51–74 age group of patients with CH-B and CH-C than in the 36–50 and 19–35 age groups of patients with hepatitis and also worse in the 41–55 and 56–81 age groups in patients with LC than in the 23–40 age group. In another study, increasing age of individuals worsened sleep quality. Increasing age was associated with less sleep quality (14).

In the elderly population, sleep quality may deteriorate, depending on physical disorders of which their frequency increases with age, drug usage, sleep disorders, or changes in lifestyle (15). Furthermore, our study revealed that sleep quality was observed to be worse in female patients with CH-B, CH-C, and LC than in male patients. A difficult marriage, a second work, or a familial burden absolutely reduces the sleep quantity and deteriorates the circadian rhythm (16).

The fact that the sleep quality of unemployed patients with CH-B and CH-C was worse than that of employed patients may show us that the reason is a decrease in functional efficiency. Though there was no significant difference in average PSQI scores in patients with hepatitis and cirrhosis from the education status variable, sleep qualities in primary school and high school graduates were worse than those who had a bachelor's or master's degree. An increase in the education level may enable individuals to be less affected from external factors, to develop conscious coping mechanisms, to see in a more realistic way the problems, such as the diseases/symptoms, and thus to have a better sleep quality (17). Sari et al. (18) showed that patients with higher levels of education comply better with the treatment.

In patients with LC, we observe that sleep quality in patients with cirrhosis receiving treatment for 72–396 months long was significantly worse than those receiving treatment for 25–60 months from the treatment duration variable point of view. In LC, complications that appear with the advance of the disease, such as itching, jaundice, hemorrhages, hepatic encephalopathy, and osteoporosis, may cause the deterioration in sleep qualities (19).

With respect to our study, there was no significant difference between patients using antiviral drugs and those who do not among patients with hepatitis and cirrhosis. Notwithstanding, it was determined that sleep qualities in patients with hepatitis using antiviral drugs were worse than those who did not use. It was concluded in the study performed by Carlson et al. (20) in which different antiviral drugs were administered to hepatitis C that antiviral drugs caused effects, such as myalgia and anorexia, and thus lead to sleep disorders.

In our study, we observed that patients with CH-B and CH-C who have hypertension as an additional disease had worse

sleep qualities than those who do not have hypertension. In addition to these factors, the presence of an additional disease in our patients caused their sleeping mode to be affected (21). Sleep qualities of our patients using antihypertensive drugs were concluded to be worse than those who did not use antihypertensive drugs. Yilmaz et al. (22) showed that beta-blockers, such as metoprolol, which is used in the treatment of hypertension, deteriorate the sleep quality.

We observed in our study that sleep quality in patients with hepatitis and cirrhosis who also had COPD was worse than those who had no COPD. It was shown in the study by Cinar and Olgun (23) that signs, such as cough and phlegm in patients with COPD, caused sleep disorders in patients.

Our study revealed that patients with hepatitis C had higher BDS scores than those with hepatitis B, and patients with cirrhosis had higher than those with hepatitis B and C. PSQI scores were higher in patients with hepatitis C than in those with cirrhosis and higher in patients with cirrhosis than in those with hepatitis B. It was observed that 48.6% of 107 patients infected with CH-B and CH-C had at least one psychiatric disorder, and that 15% of the patients met the major depression criteria. Moreover, in the same study, there was no statistically significant difference in patients with CH-B and CH-C from the psychiatric diagnosis rates point of view; however, scores of quality of life in both groups were found to be significantly lower than those in the control group. It was observed that psychiatric comorbidity, particularly depression, was the most important variable that reduced the quality of life (24). In the study performed by Ozkan et al. (11), both the CH-B and CH-C groups had patients with mild depression.

Mechanisms lying under the fact that chronic hepatitis B virus (HBV) was less associated with psychiatric symptoms are still under examination. Some studies indicate the differences related to the viruses. It was suggested that hepatitis C virus has direct neurotoxic effect in the brain, the same as human immunodeficiency virus, and therefore, its neuropsychiatric effects are greater. However, a similar observation could not be done in patients with HBV (25, 26). Our study further revealed that sleep quality was bad in patients with cirrhosis. Montagnese et al. (27) reported that sleep wave anomalies are recorded in patients with cirrhosis.

The limitations of our study include a small size patient group.

In conclusion, we observed that our patients with cirrhosis had mild depression according to BDS evaluation. The fact that the signs of the disease appear more severe in patients with LC and hepatitis C in our study than in patients with hepatitis B and reasons, such as poor prognosis of disease, may increase the tendency to depression. We found that patients' sleep qualities are meaningfully worse in elderly patients with hepatitis, female patients who do not have a job and taking antidepressant medicines, patients who have hypertension and taking antihypertension medicines, patients who have chronic lung diseases, and cirrhosis patient groups that have been treated for a long time than in other groups. In addition, there was a positive relationship between sleep quality and depression levels in CH-B, CH-C, and LC. CH-B, CH-C, and LC are important health problems, which can affect the individual and the people around him/her bodily, socially, and psychologically. Education and psychiatric approach are key factors in the treatment and follow-up of these diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from Istanbul Provincial Health Directorat (Approval Date: 17.02.2015, Approval Number: 156).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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Original Article

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Effects of Alprazolam and Clonazepam on Blood Sugar in Patients with Panic Disorder

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BACKGROUND/AIMS
Panic disorder is one of the most common anxiety disorders with a good pharmacotherapeutic response. Benzodiazepines are one type of such efficient medications. This study aimed to evaluate the impact of alprazolam and clonazepam on blood sugar of adults with panic disorder.

MATERIAL and METHODS
This randomized controlled trial recruited 45 patients suffering from panic disorder. After filling out the initial questionnaire and measuring patients' height and weight, fasting and 2-hour postprandial blood sugar and glycosylated hemoglobin (HgAlc) were measured. Then, the patients were randomly allocated into three groups of sertraline, sertraline+alprazolam, and sertraline+clonazepam. After 3 months of treatment, the lab tests were repeated, and the data were analyzed using the statistical analysis software SPSS 18.

RESULTS
A total of 32 women and 13 men with a mean age of 28.98±6.8 years were recruited. Demographic characteristics and history of physical and psychological diseases did not show any significant differences among the three groups (p>0.05). At the end of the 3rd treatment month, the mean of 2-hour postprandial blood sugar (p=0.032) and HgAlc (p=0.0007) were decreased in the sertraline group, while the mean level of fasting blood sugar (p=0.006) and 2-hour postprandial blood sugar (p=0.015), and HgAlc (p=0.015) revealed a significant increase in the sertraline+alprazolam group.

CONCLUSION
This study showed that the treatment with alprazolam can cause an increase in the blood glucose in non-diabetic patients suffering from panic disorder.

Keywords: Alprazolam, blood sugar, clonazepam, panic disorder

INTRODUCTION

As a common anxiety disorder, panic disorder has a prevalence ranging from 1% to 2% in the lifetime of the general population (1). Pharmacotherapy and cognitive psychotherapy are the two effective treatment methods (2). Benzodiazepines are among the fast-acting anti-panic medications that can be used in a short-term and long-term treatment (3-6). On the other hand, it may take up to several weeks to achieve the therapeutic effect of selective serotonin reuptake inhibitors (SSRIs), and benzodiazepines represent the best treatment option, especially in the first few weeks. Among benzodiazepines, alprazolam (Xanax) is one of the most widely used medications for panic attacks (7-9), although similar effects were reported for lorazepam and clonazepam (10). Alprazolam reaches its maximum serum concentration 1 to 2

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hours after taking a 1 mg dose, and it has a half-life of 9–16 hours (11). Alprazolam randomly binds to benzodiazepine GABA receptors (12) to reduce the general brain activity. In addition, the GABA system interacts with other neurotransmitters, including serotonergic, adrenergic, cholinergic, and opioid systems. The clinical effects of alprazolam in treating anxiety and depression occur through the interaction of alprazolam with serotonergic and adrenergic pathways in the limbic system, brain stem, and locus coeruleus (8). Like other benzodiazepines, clonazepam exerts its effect by binding to GABA receptors, and thus increases the inhibitory activity of this receptor (13). Previous studies have shown that clonazepam has significantly greater effects than placebo in the treatment of panic attack (14-16).

In addition to their psychological effects, benzodiazepines exert different metabolic effects (17-20). Many studies have investigated the metabolic effects of alprazolam on blood sugar levels in humans, and given the conflicting results they produced and because of the widespread use of alprazolam and clonazepam in the treatment of panic disorder, the present study aims to assess the effect of these medications on blood sugar levels in non-diabetic individuals suffering from panic disorder.

MATERIALS and METHODS

In the present randomized controlled trial, 45 patients visiting psychiatric departments affiliated to Babol University of Medical Sciences (Rouhani and Yahyanejad Hospitals) were randomly enrolled if they presented with diagnostic criteria for panic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), as well as the study inclusion criteria.

The study inclusion criteria included the age ≥18 years and older, a written consent form, psychiatric diagnosis of panic disorder based on the DSM-IV criteria (newly diagnosed patients), no intention of pregnancy during the study and using a suitable contraceptive method, and no use of psychoactive medications over the week.

The study exclusion criteria included active suicidal ideations; diseases in which sertraline, alprazolam, and clonazepam are contraindicated; a history of or current psychotic or bipolar disorder; pregnant or breastfeeding women, uncontrolled seizure disorder; a personality disorder that impairs assessment of treatment efficacy and safety, simultaneous treatment with psychotropic medications, and diabetes.

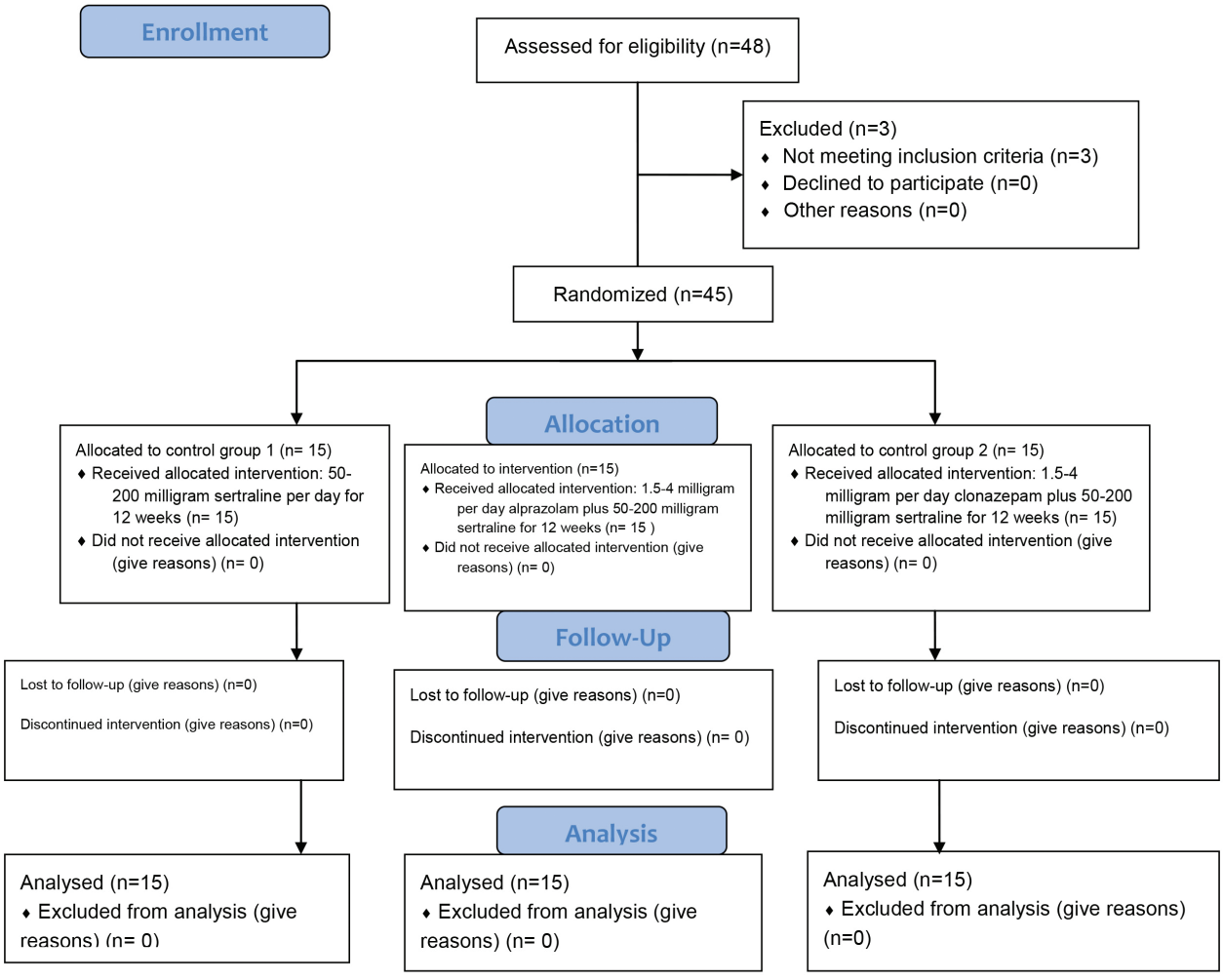

FIGURE 1. CONSORT 2010 flow diagram

First, participants' demographic details (age, gender, education level, and marital status), history of physical and psychoneurological diseases, and frequency of panic attacks over the last week were recorded. Then, their height and weight were measured, and fasting and two-hour postprandial (2hpp) blood sugar, and HbAlc were assessed. Patients were randomly (in numerical order) allocated to sertraline, sertraline plus alprazolam, and sertraline plus clonazepam groups (15 patients in each group). Figure 1 presents the study process flowchart.

The case group (sertraline+alprazolam) received a daily dose of 1–2 mg of alprazolam plus 50 mg to 200 mg of sertraline (depending on patient's response), and the control group (sertraline only) received 50 mg to 200 mg of sertraline per day. Considering that in newly diagnosed patients, the control of panic attacks (especially in the first weeks of treatment) is difficult, 0.5 mg alprazolam was prescribed if required in case of a panic attack. The other control group (sertraline+clonazepam) received a daily dose of 0.5–1 mg of clonazepam plus 50 mg to 200 mg of sertraline. Patients were studied over 12 weeks. At this stage, patients for whom a medical visit was necessary have been visited by the project psychiatrists, free of charge. At the end of the first treatment month, patients' body mass index was measured again, they were visited by the psychiatrist, and the frequency of their panic attacks was recorded. At the end of the 3rd treatment month, patients were visited by the psychiatrist, and their fasting and 2-hour postprandial blood sugar and HbAlc were evaluated again.

The ethics committee approval was received for this study from Babol University of Medical Sciences, Babol, Iran (Approval date: December 28, 2015; Approval number: Mubabol.Rec.1394.255). All participants provided an written informed consent form.

This study was registered on the website of clinical trials (www.irct.ir) with the registration ID: IRCT2016040722991N3.

Statistical Analysis

Data obtained from the three groups were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Statistics version 18 (SPSS IBM Corp.; Armonk, NY, USA). Chi-square and analysis of variance (ANOVA) tests have been used for data analysis; in addition to the ANOVA, repeated measure (general linear model) was used to assess the trend of blood glucose and HbAlc changes. Some of baseline variables such as drug dose have been considered as covariates in this analysis model. A p-value <0.05 was considered statistically significant.

RESULTS

Patients' mean age was 28.98±6.8 years (range, 19–52 years). A total of eight patients were unable to complete the treatment course (due to medication side-effects or non-attendance). Physical diseases were reported by 31.1% of patients. Of all physical diseases reported, the mitral valve prolapse at 11.1% was the most frequent among patients with panic attack. Furthermore, 48% of patients had psychiatric comorbidities, of which, GAD at 17.7% and adjustment disorder at 11.1% had the highest prevalence. Other comorbidities were major depressive disorder, social phobia, OCD, and dysthymia, respectively. The mean number of panic attacks in the last week was 2.98±1.8, which was reduced to 1.42±0.5 after the first month of treatment and zero by the end of the 3rd month. This reduction was statistically significant (p=0.002). Table 1 presents the blood sugar status of patients with panic attack before and after treatment in the sertraline, sertraline+alprazolam, and sertraline+clonazepam groups.

Figure 2 shows therapeutic effects of the three groups on HgAlc before and after the intervention. No significant dose-dependent effects were observed (p=0.807).

In terms of side-effects, 37 (82.7%) patients experienced at least one side-effect, and the sertraline+alprazolam group had the highest side-effects; although generally, no significant difference was observed among the groups in terms of medication side-effects (p>0.05). The most common side-effect was loss of appetite, as 44% of patients (four from sertraline group and three from sertraline plus clonazepam) experienced it. Meanwhile, 56% (eight from the sertraline+alprazolam group and one from the sertraline+clonazepam group) experienced increased appetite. No significant association was observed between se-

TABLE 1. Blood sugar profile of patients with panic attack before and after treatment in the sertraline, Sertraline+Alprazolam, and Sertraline+-Clonazepam groups

Variable	Treatment Group	Baseline Mean±SD**	After 3 Months Mean±SD	p
Fasting blood sugar	Sertraline	88.60±11.5	89.40±11.4	NS*
	Sertraline+alprazolam	86.20±10.7	89.62±10.0	0.006
	Sertraline+clonazepam	85.33±10.2	86.00±9.6	NS*
	p	0.69	0.62	-
2hpp*** blood sugar	Sertraline	101.80±11.1	97.50±10.4	0.032
	Sertraline+alprazolam	97.67±13.8	102.69±15.5	0.015
	Sertraline+clonazepam	96.93±12.6	99.00±8.6	NS*
	p	0.52	0.56	-
Hb****Alc	Sertraline	5.12±0.3	4.72±0.2	0.007
	Sertraline+alprazolam	5.20±0.5	5.45±0.4	0.015
	Sertraline+clonazepam	5.06±0.4	4.96±0.2	NS*
	p	0.69	0.0001	-

*NS: nonsignificant; **SD: standard deviation; ***2hpp: 2-hous post-prandial; ****Hb: hemoglobin

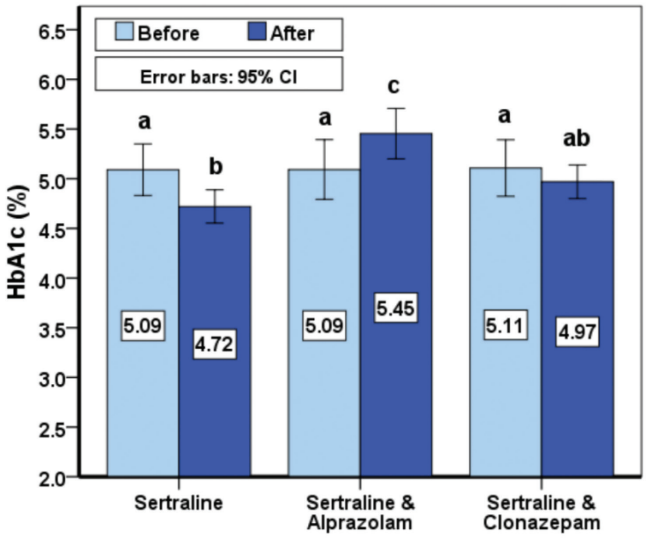

FIGURE 2. Effects of the three treatment groups on HbAIc (before and after the intervention)

rum glucose changes and weight gain (p>0.05). Hypersomnia and sexual dysfunction were other common side-effects.

DISCUSSION

The present study showed a significant reduction in the 2-hour postprandial blood sugar (p=0.032) and HbAIc (p=0.007) in the sertraline group, and a significant increase in fasting (p=0.006) and 2-hour postprandial (p=0.015) blood sugar and HbAIc (p=0.015) in the sertraline+alprazolam group.

Surwit et al. (21) compared the effects of 5 mg/kg injection of alprazolam with placebo in diabetic rats and reported that alprazolam can increase plasma insulin and reduce blood glucose in response to stress. The difference between their results and ours appear to be caused by the fact that these authors assessed only the short-term effect of alprazolam on diabetic rats.

In a study by Lustman et al. (22), alprazolam reduced HbAIc over 8 weeks in diabetic patients with panic attack. Unlike the present study, their study was conducted on diabetic patients with uncontrolled blood sugar. Moreover, they assessed only the effect of alprazolam alone without sertraline, which can explain the difference in the results.

In a clinical trial conducted by Afkhami Ardekani et al. (23), the administration of fluoxetine led to significant reductions in blood sugar indices, including fasting and postprandial blood sugar and HbAIc. The same result was observed in the present study for sertraline. Unlike the present study, in the Afkhami study, alprazolam led to reduced fasting and postprandial blood sugar and HbAIc. Interestingly, their study population also had uncontrolled diabetes and had received alprazolam alone.

In another study, Afkhami investigated the effect of alprazolam on blood sugar control in diabetic patients and reported reduced fasting blood sugar (24). In the present study, the therapeutic effects of alprazolam and fluoxetine were compared, while we assessed the effect of sertraline+alprazolam as a treatment approach to panic disorder. The difference might be attributed to the study design (to use different SSRIs as treatment options) and the effect of sertraline on pharmacodynamics of alprazolam. Given that sertraline is an inhibitor of liver enzymes, especially cytochrome P450 (25), it can exert its effect by changing hepatic uptake and metabolism of alprazolam, and provide its different impact on blood glucose.

In a study by Gomez et al. (26), administration of sertraline led to no increase in blood sugar following glucose injection in both diabetic and non-diabetic groups of rats, and clonazepam caused no significant change in fasting and postprandial blood sugar in rats. The present study confirmed this finding as sertraline-reduced postprandial blood sugar and HbAIc, but clonazepam caused no significant change in blood sugar indices.

In 1977, Zumoff and Hellman (27) revealed that daily intake of 40 mg of chlordiazepoxide in insulin-dependent diabetic women exacerbated hyperglycemia and increased fasting blood glucose from 220 to 380. They also asserted that most analgesics exacerbate hyperglycemia and most antidepressants improve hyperglycemia. The present study results showed increased fasting blood sugar, 2hpp, and HbAIc levels. Since the fasting blood sugar level is not a reliable criterion for long-term blood sugar control, HbAIc appears to be a more appropriate criterion for the assessment of the alprazolam effect.

In another review study, McIntyre et al. (28) investigated the effect of antidepressants on blood sugar hemostasis and insulin sensitivity, and the showed that certain serotonergic medications such as fluoxetine reduce hyperglycemia and increase insulin sensitivity, while noradrenergic antidepressants such as desipramine have the reverse effect. Moreover, norepinephrine and serotonin reuptake inhibitors such as venlafaxine and duloxetine have no effect on blood sugar hemostasis.

In a clinical trial, Giardino et al. (29) investigated the effect of alprazolam on the neuroendocrine reaction of the body in response to hypoglycemia 120 minutes after administration. The results showed that alprazolam reduces ACTH and GH response to ITT-induced hypoglycemia butthat it has no effect on the level of cortisol. Alprazolam showed no effect on the hypoglycemia-induced glucose changes. In a similar study, Patel et al. (30) observed an increase in cortisol and ACTH due to hypoglycemia in the placebo group, but not in the alprazolam group. The results of a study by Hedrington et al. (31) also confirmed the effect of alprazolam in reducing hypoglycemia-induced neuroendocrine effects in healthy people. However, the above studies investigated the acute effect of medication on fasting and postprandial blood sugar, but they did not measure HbAIc. It appears that alprazolam affects neuro-adrenergic systems in the short-term, inhibits them, and prevents blood sugar increase.

In the present study, sertraline was a fixed component of treatment in all three groups, and its blood-sugar-reducing effect was demonstrated. However, this effect was not observed in combination with alprazolam, and the blood sugar increased. The reason for the difference may be attributed to the combined use of sertraline and alprazolam as this combination changes its pharmacodynamics and its metabolism and can ultimately lead to increased blood sugar levels.

One of the side-effects of alprazolam is impaired appetite. In the present study, this effect was observed as increased appetite in the sertraline+alprazolam group. The increase in appetite can be due to the direct effect of medication on the appetite center, or due to a sense of well-being and an improved clinical status.

The weight gain was also proposed as another side-effect of alprazolam. The sedation and lethargy induced by alprazolam can lead to inactivity or reduced physical activity, and in the long term, it can lead to weight gain and its subsequent complications, including insulin resistance.

Another significant clinical point in the present study was the lack of a significant change in the blood sugar profile in patients receiving clonazepam+sertraline. Compared to alprazolam, clonazepam appears to be a better treatment choice, especially for diabetic patients.

One of the strength points of the present study is the fact that many studies have assessed the effect of benzodiazepines such as alprazolam on the blood sugar profile of diabetic patients, but only a few studies have been conducted in non-diabetic patients. Another distinctive point in the present study was the assessment of a combined use of alprazolam+sertraline, while most studies have investigated the effect of alprazolam alone.

Limitations of this study included the difficulty of panic attacks control in the control group, especially in the first weeks of treatment when we prescribed 0.5 mg alprazolam, as needed, in persistent panic attacks that did not respond to sertraline. It is suggested to future researches to design the study using a method in which the control group does not need benzodiazepines, although it seems very difficult.

The present study showed that alprazolam can increase HbAlc and thus affect the control of blood sugar in non-diabetic patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Babol University of Medical Sciences, Babol, Iran (Approval date: December 28, 2015; Approval number: Mubabol.Rec.1394.255).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author contributions: Concept – A.A.M., S.M.; Design – A.A.M., S.M.; Supervision - A.A.M., S.M.; Resource - A.A.M., S.M.; Materials – A.A.M., S.M., N.T., M.S., A.H., M.M.; Data Collection and/or Processing – A.A.M., S.M., N.T., M.S., A.H., M.M.; Analysis and/or Interpretation – A.A.M., S.M., A.B.; Literature Search – A.A.M., S.M., N.T.; Writing - A.A.M., S.M.; Critical Reviews- A.A.M., S.M.

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Original Article

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Effects of Low-Frequency Electromagnetic Fields on Chondrocytes in Short-Term Cultures

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BACKGROUND/AIMS
Tissue engineering approaches have provided treatment options for patients with limited cartilage repair capacity. Most of these approaches rely on isolating and expanding chondrocytes in vitro. Mechanical stress, ultrasound, and electric and electromagnetic fields (EMFs) can be used to stimulate cartilage repair. EMF has been used in the management of conditions such as arthritis and fractures. Most of the previous studies have focused on low-frequency pulsed EMF (PEMF). The aim of the present study was to investigate the effects of low-frequency continuous (sinusoidal) EMF (CEMF) versus PEMF on chondrocytes.

MATERIAL and METHODS
Chondrocytes from bovine nasal cartilage were exposed to low-frequency CEMF versus PEMF, and the proliferation and differentiation capacities of these chondrocytes were determined. The effects of EMFs on retinoic acid receptor beta and transforming growth factor beta (TGF-β) expressions were investigated using quantitative reverse transcription polymerase chain reaction.

RESULTS
Our observations suggested that there was no difference between the effects of PEMF and CEMF exposure on the proliferation and differentiation capacities of chondrocytes.

CONCLUSION
EMF-mediated proliferation of chondrocytes requires the presence of growth factors, especially insulin-like growth factor, in the environment to maintain the chondrogenic phenotype; furthermore, the EMF effect on chondrocytes is independent of TGF-β.

Keywords: Chondrocyte, electromagnetic field, growth factor, retinoic acid receptor

INTRODUCTION

Mechanical stress, ultrasound, and electric and electromagnetic fields (EMFs) can be used to stimulate cartilage repair by increasing cell proliferation and matrix synthesis. In the last few decades, numerous *in vitro* and *in vivo* studies have been conducted on pulsed EMF (PEMF) applied to cells from different species (1-3). Variable responses of chondrocytes to PEMF have been reported, as the studies have used diverse techniques (4, 5). However, the biological effects of PEMF and the underlying mechanisms of these effects are ill-defined. Because most of the exposure of humans in the natural environment is to low frequencies (20–120 Hz) of continuous (sinusoidal) EMF (CEMF), a study that investigates the effects of CEMF and PEMF on human cells is required. To our knowledge, there are few studies comparing the effects of different types of EMF (CEMF vs. PEMF).

Articular cartilage is composed of chondrocytes embedded in an extracellular matrix (ECM) of principally type II collagen and proteoglycan aggrecan molecules. On the other hand, collagen type I is often considered an indicator of fibrocartilage and dedifferentiation of chondrocytes to fibroblast-like cells (6). Chondrocytes can easily proliferate and produce ECM in a growth factor-supplemented medium. Several growth factors such as fibroblast growth factor-2 (FGF-2), insulin-like

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growth factor I (IGF-I), transforming growth factor beta (TGF-β), and retinoic acid (RA) have been shown to be essential for the expansion of chondrocytes and the maintenance of their chondrogenic capacity (7-9). Endogenously produced growth factors, such as TGF-β and IGF-I, increase cartilage-specific gene expression in chondrocytes (7, 8). FGF-2 has been shown to enhance the proliferative and redifferentiation capacity of mature chondrocytes and the chondrogenic capacity of human mesenchymal stem cells (10, 11). RA, an active vitamin A metabolite, acts through its receptors (retinoic acid receptors, RARs). RARs act as ligand-activated transcription factors and participate in the growth and differentiation of several tissues including cartilage (2_ENREF_5, 12-14). RA and TGF-β signaling have been shown to interact during chondrogenesis in several systems (12, 14). Kafienah et al. (15) have highlighted the importance of these receptors in chondrogenesis by using antagonists against the receptors. Li et al. (16) have reported a decrease in TGF-β protein levels with the addition of a retinoic acid receptor beta (RARβ) inhibitor, suggesting a synergistic interaction between TGF-β and RA in chondrogenesis. However, limited data are available on the interaction of other growth factors with RA receptors.

In the present study, the effects of low-frequency CEMF versus PEMF on chondrocyte proliferation and differentiation capacities *in vitro* were investigated and the question whether the effects of EMFs occur through RARβ and TGF-β or not was asked.

MATERIALS and METHODS

Isolation of Chondrocytes from Cartilage

Full-thickness bovine nasal cartilage obtained from a local abattoir was harvested aseptically from adult animals (n=5; age, 16–20 months). Ethics committee approval was received for this study from the Adnan Menderes University Animal Ethics Committee (Approval Date: 24.06.2005, Approval Number: 010-017) and the abattoir gave permission for the use of cartilage tissue. Freshly dissected cartilage from individual animals was cut into slices of 5 cm×1.5 cm×2 mm using a scalpel. The slices were washed once with sterile phosphate-buffered saline (Sigma, Darmstadt, Germany) for 20 min. Chondrocytes were isolated from the cartilage through sequential digestion at 37°C for 15 min with 1 mg/mL of testicular hyaluronidase (Sigma), 0.25% w/v trypsin (Sigma) for 30 min, and 1.5 mg/mL of clostridial collagenase (Sigma) in an expansion medium comprising Dulbecco's Modified Eagle's Medium (DMEM; Sigma) containing 10% (v/v) fetal calf serum overnight on an orbital shaker. Isolated chondrocytes were centrifuged and resuspended in an expansion medium containing 100 U/mL penicillin and 100 μg/mL streptomycin (Sigma). Cells were counted using a hemocytometer, plated in 24-well plates (Nunc, Denmark) in monolayer (1×10^5 cells/cm^2), and cultured to equilibrate for 48 h at 37°C in a humidified atmosphere of 5% CO_2/95% air.

Culture of Chondrocytes and Exposure to EMF

Chondrocytes were cultured to reach confluence for 48 h and then exposed to EMF and growth factors for 7 days. During EMF treatment experiments, cells were cultured with DMEM, 100 U/mL penicillin, 100 μg/mL streptomycin, and 2 mM glutamine without fetal bovine serum. Growth factors were added as 10 ng/mL IGF (Sigma) and 50 ng/mL FGF-2 (Sigma). Growth factor concentrations used in the study were determined as described in the literature (17). Cells were exposed to either CEMF or PEMF in the absence or presence of growth factors for 30 min/day for 7 days at room temperature and then replaced back into the incubator. Non-EMF exposed cells were also treated the same way, except EMF application. Before EMF application, optimal EMF dose that can drive maximum cell proliferation was determined by searching the literature (3, 18, 19). It is difficult to characterize the specific beneficial EMF dose due to the broad range of intensity reported in the literature and the external condition effects. EMFs ranging from 1 to 3 mT appear to generate positive results on the cartilage.

During cell cultures, chondrocytes were exposed to CEMF or PEMF in the north–south direction. Three study groups were defined: (1) CEMF group, (2) PEMF group, and (3) control group. Chondrocytes cultured in the absence of growth factors and EMF were used as the negative control group. The control group was maintained at identical conditions, except for CEMF or PEMF exposure. The reason for applying 30 min exposure to EMF was to determine whether a short-term treatment with the growth factors has transient or persistent influence on chondrocytes. Figures 1a and b show the CEMF and PEMF exposure setup, respectively. After 7 days in culture, the pro-

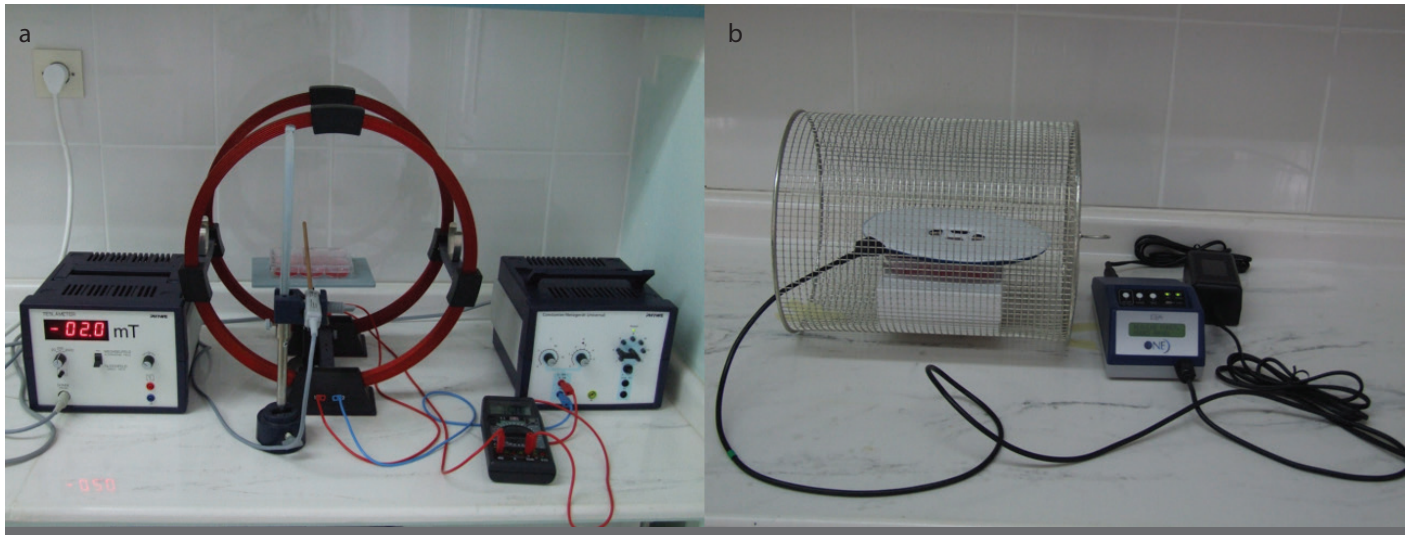

Figure 1. a, b. Photographs of CEMF (a) and PEMF (b) bioreactors and the experimental design used in our study. Chondrocytes were exposed to 2 mT and 50 Hz (30 min/day) for CEMF exposure (a) and 75 Hz and 2.3 mT (30 min/day) for PEMF exposure for 7 days
CEMF: continuous electromagnetic field; PEMF: pulsed electromagnetic field

liferation capacity of cells was determined by counting them using a hemocytometer. Cell samples were also collected and stored in RNAlater solution (Ambion; Thermo Fisher Scientific, Inc, Waltham, MA, USA) accordingly for further molecular analyses.

CEMF Exposure Conditions

Cultures were exposed to 50 Hz CEMFs in the north–south direction. CEMF was generated by a pair of Helmholtz coils, each having 154 turns and carrying a maximum of 5 A, with a resistance of 2.1 Ω. The coils were separated by a distance of 40 cm, equal to the radius of the coil, with a maximum flux density for I=5 A in a Helmholtz array of 3.5 mT (Phywe, Germany). Chondrocytes were exposed to 50 Hz and 2 mT EMF (30 min/day) for 7 days. Intensities of CEMF between the two circular coils were monitored during the experiments using a digital gaussmeter/teslameter (Model 7030, F.W. Bell, Syprus, Orlando, FL, USA). Multiwell plates were placed in the mid-plane between the two coils at a point where theoretical calculations showed a uniform magnetic field (Figure 1a).

PEMF Exposure Conditions

Pulsed EMF exposure apparatus consisted of a pair of Helmholtz coils placed opposite to each other and in a signal generator (IGEA, Carpi, Italy) (Figure 1b). Multiwell plates were placed between Helmholtz coils so that the plane of the coils was perpendicular to the plates. The pulsed signal parameters were as follows: pulse duration, 1.3 ms; magnetic field intensity, 2.3 mT; induced electric field, 2 mV; frequency, 75 Hz; and yielding duty of cycle, 1/10. Chondrocytes were exposed to PEMF (30 min/day) for 7 days. Intensities of magnetic fields were measured using a digital gaussmeter/teslameter (Model 7030, F.W. BELL, Syprus). The magnetic field was uniform and focused on the plates placed between the two coils.

RNA Isolation and Reverse Transcription

Total RNA was prepared from chondrocytes (obtained from 5 animals, each analyzed individually) using the RNeasy Mini Kit (Qiagen, Hilden, Germany). RNA quality at $OD_{260/280}$ of the samples was checked using Qubit fluorometer (Thermo Fisher Scientific). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to quantify mRNA levels for collagen type I (dedifferentiation marker), collagen II and aggrecan (chondrogenic markers), and TGF-β and RARβ in cultured chondrocytes (13, 15). Briefly, cDNA was generated using reverse transcriptase (Promega, UK). PCRs were performed using SYBR® Premix Ex Taq™ (Takara, Gennevilliers, France) and monitored using Rotor-Gene 6000 Real-Time PCR system. Primer sequences for TGF-β were as follows: forward 5′-CTGCTGAGGCTCAAGTTAAAAGTG-3′ and reverse 5′-CAGCCGGTTGCTGAGGTAG-3′. The cycle conditions for PCR and sequences of the primers for type I and II collagens, aggrecan, and RARβ were as previously described (13, 15). The expression levels for the genes of interest were normalized to β-actin.

Statistical Analysis

Statistical analyses were performed using analysis of variance. Data were expressed as mean ± SEM. A p value of <0.05 was considered as statistically significant.

RESULTS

Effects of EMF Exposure and/or Growth Factors on Chondrocyte Proliferation Rate

The effects of EMF exposure and growth factor treatment on chondrocyte proliferation are summarized in Figure 2. On day 0, equal numbers of cells were placed in wells (5×10^5/well). In the control group, an increase (×2.6) in the chondrocyte number was observed in the absence of EMF or growth factors on day 7. Applied on its own, EMF's effect on cell proliferation was negligible compared with that in the control group. Both growth factors, especially FGF-2 (p=0.038), stimulated chondrocyte proliferation significantly. Additionally, IGF and FGF-2 led to a 4–6 times increase in the cell number. The combination of EMF (whether continuous or pulsating) and growth factors led to a significant increase in the proliferation rate of the cells (Figure 2). This effect was most pronounced in the presence of FGF-2 (p=0.005).

Effects of EMF Exposure and/or Growth Factors on the Synthesis of Cartilage Proteins

The effects of EMF exposure and/or growth factor treatment on cartilage protein syntheses are summarized in Figure 3. mRNAs were isolated from the chondrocytes cultured in monolayers for 7 days and analyzed using qRT-PCR for collagens type I (Figure 3a) and type II (Figure 3b) and aggrecan (Figure 3c). Type II collagen expression was lower in cells treated with IGF-I (10 ng/mL) or FGF-2 (50 ng/ml) than in controls. Both PEMF and CEMF caused an increase in type I collagen expression. IGF-I reversed PEMF's stimulatory effects on type I collagen expression, whereas FGF-2 exerted effects similar to those of CEMF. Aggrecan expression was also differentially affected by PEMF in the presence or absence of the growth factors FGF-2 or IGF-I (Figure 3c).

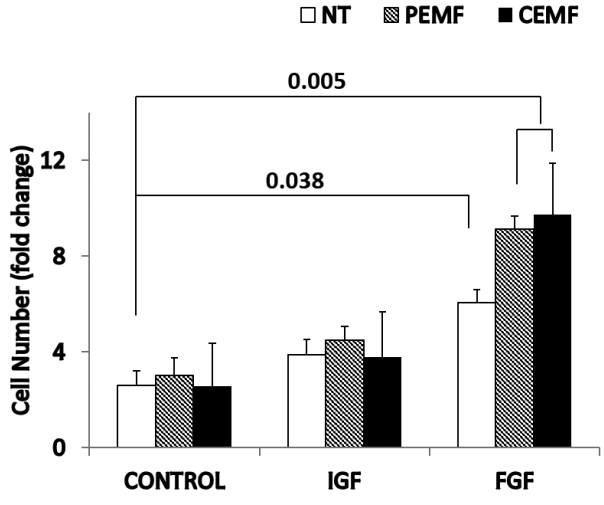

Figure 2. Effects of EMF and growth factors on chondrocyte proliferation in monolayer cell cultures. The fold change in cell number in each plate on day 7 was compared with the cell number seeded on plates on day 0. Results are expressed as mean ± SEM (n=5). A p value of <0.05 was accepted as significant using ANOVA
EMF: electromagnetic field; SEM: standart error of mean; NT: untreated; CEMF: continuous electromagnetic field; PEMF: pulsed electromagnetic field;

Effects of EMF and/or Growth Factors on TGF-β and RARβ Expressions

TGF-β plays a critical role in chondrogenesis. Therefore, we questioned whether exposure to EMF induces a change in endogenous TGF-β expression. IGF and FGF-2 have been reported to crosstalk with TGF-β (20). CEMF and PEMF were applied in the absence or presence of IGF and FGF. As shown in Figure 4, a significant increase in TGF-β expression was observed when growth factors were used in combination with EMF applications. Interestingly, the effects of EMF on TGF-β expressions were growth factor and/or EMF type dependent. While the combination of CEMF with IGF-I has a maximum stimulatory effect on TGF-β expression, this effect was reversed when CEMF was combined with FGF-2. On the other hand, the combination of FGF-2 with PEMF caused a significant increase in TGF-β expression (Figure 4).

In cultures, RARβ expression was differentially affected by growth factors and/or EMF exposures (Figure 5). RARβ expression decreased when chondrocytes were treated with EMF, applied alone. IGF-I also caused a decrease in RARβ expression on its own. On the other hand, FGF-2 caused a significant increase in RARβ expression, with the increase being most prominent in combination with PEMF (Figure 5).

DISCUSSION

Recent interest in the use of mechanical stimulation such as EMF application has made it necessary to understand how these agents regulate gene expression in connective tissue cells.

EMF is one of the most treated therapeutic alternatives on tissue repair. It exerts positive effects on tissue metabolism through hyperemization (21). The piezoelectric structure of the ECM of hyaline cartilage allows the conversion of electromagnetic oscillations to mechanical vibrations and vice versa (22). Reportedly, EMF treatment improves suboptimal or degenerate cellular conditions in chondrocytes (23). Furthermore, we are constantly exposed to low-frequency CEMF at home as well as at work by technological processes. In clinical practice, due to their positive effects, EMFs are used in various instruments.

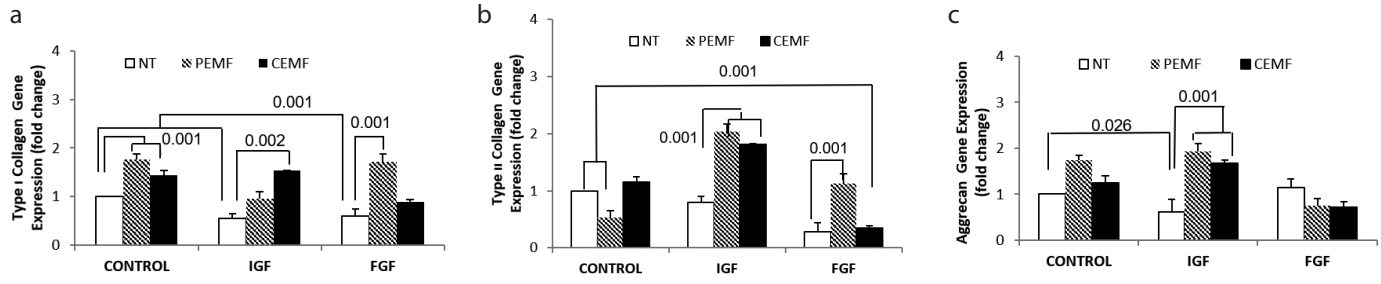

Figure 3. a-c. Quantitative mRNA analysis of cartilage matrix proteins in bovine nasal chondrocyte cultures. Chondrocytes in monolayer were incubated with/without 10 ng/mL IGF, 50 ng/mL FGF-2, and/or PEMF and CEMF for 7 days. Total RNA was harvested at the end of the culture period and analyzed using qRT-PCR for mRNA of type I collagen (a), type II collagen (b), and aggrecan (c). mRNA expression is shown as the relative change over untreated chondrocyte controls. Results are expressed as mean ± SEM (n=5). A p value of <0.05 was accepted as significant using ANOVA. Detailed methodology has been presented in the materials and methods section
CEMF: continuous electromagnetic field; PEMF: pulsed electromagnetic field; SEM: standart error of mean; NT: untreated; IGF: insulin-like growth factor; FGF: fibroblast growth factor

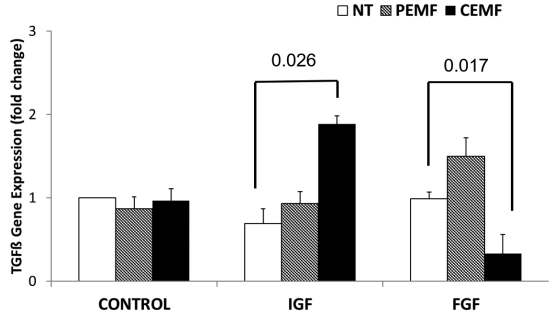

Figure 4. Quantitative mRNA analysis of TGF-β in monolayer bovine nasal chondrocyte cultures. Chondrocytes in monolayer were incubated with/without 10 ng/mL IGF, 50 ng/mL FGF-2, and/or PEMF and CEMF for 7 days. Total RNA was harvested at the end of the culture period and analyzed using qRT-PCR for mRNA of TGF-β. mRNA expression is shown as the relative change over untreated chondrocyte controls. Results are expressed as mean ± SEM (n=5). A p value of <0.05 was accepted as significant using ANOVA. Detailed methodology has been presented in the materials and methods section
CEMF: continuous electromagnetic field; PEMF: pulsed electromagnetic field; NT: untreated; SEM: standart error of mean; IGF: insulin-like growth factor; FGF: fibroblast growth factor

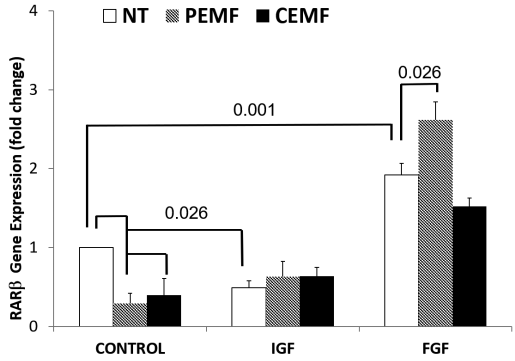

Figure 5. Quantitative mRNA analysis of RARβ in monolayer bovine nasal chondrocyte cultures. Chondrocytes in monolayer were incubated with/without 10 ng/mL IGF, 50 ng/mL FGF-2, and/or PEMF and CEMF for 7 days. Total RNA was harvested at the end of the culture period and analyzed using qRT-PCR for mRNA of RARβ. mRNA expression is shown as the relative change over untreated chondrocyte controls. Results are expressed as mean ± SEM (n=5). A p value of <0.05 was accepted as significant using ANOVA. Detailed methodology has been presented in the Materials and Methods section
CEMF: continuous electromagnetic field; PEMF: pulsed electromagnetic field; NT: untreated; IGF: insulin-like growth factor; FGF: fibroblast growth factor; RARβ: retinoic acid receptor beta

In the present study, data on the effects of low-frequency CEMF and PEMF on bovine nasal cartilage chondrocytes in the absence or presence of either FGF-2 or IGF-I in short-term monolayer cultures were presented. CEMF was applied as 50 Hz and 2 mT EMF, whereas for PEMF, pulse duration of the signal, repetition rate, and intensity of magnetic field were 1.3 ms, 75 Hz, and 2.3 mT, respectively. Both FGF-2 and IGF-I are commonly used in tissue engineering techniques to maintain chondrogenic differentiation.

In the present study, first, the proliferation capacity of chondrocytes was monitored. Nasal chondrocytes isolated from the nasal septum have been reported to be a promising alternative cell source for cartilage tissue engineering (24). Their ECM components are similar to those of articular chondrocytes (25). Furthermore, they have been shown to respond to biomechanical stimulation like articular chondrocytes (26). Our results showed that EMF alone did not increase the proliferation capacity of chondrocytes in monolayer chondrocyte cultures. Previous studies have reported that 50 Hz EMF can enhance cell proliferation of various cell types, such as human epidermal stem cells and keratinocytes *in vitro* (27, 28). However, our findings are in agreement with those of Schmidt-Rohlfing et al. (1) who reported that 14 days of exposure to 50 Hz CEMF with a flux density up to 2 mT has no effect on human adult osteoarthritic chondrocytes. Interestingly, in our study, EMF intensified the proliferative effects of growth factors (IGF-I and FGF-2) on bovine nasal chondrocytes. EMF effect with FGF-2 was more potent than that with IGF-I (Figure 2). Thus far, we cannot say whether this effect observed with FGF-2 and EMF was an additive or a synergistic effect. On the other hand, Vincent et al. (29) have shown that PEMF increases endogenous FGF-2 release from endothelial cells in diabetic mice. This suggests a synergistic effect for EMF. Another explanation for the improved FGF-2 effect may be the induction of its receptor by EMF. Such an effect has been reported by Fitzsimmons et al. (30) showing that combined magnetic fields induce the release of IGF-II and IGF-II receptors in human osteosarcoma cell line (TE85).

Second, the effects of EMFs on mRNA expressions of type I and II collagens and aggrecan in the presence or absence of growth factors (IGF-I and FGF-2) were examined. Both growth factors have been reported to influence matrix production and deposition in cartilage. IGF-I reportedly promotes proteoglycan production in a dose-dependent manner (31). FGF-2 has been shown to increase not only the proliferation capacity of bovine articular chondrocytes but also the synthesis of glycosaminoglycans (20). We observed a decrease in type I and II collagen expressions with FGF-2 treatment, whereas no change was observed in aggrecan expression (Figure 3). There was no major difference in type I and II collagen expression levels between chondrocytes exposed to PEMF and CEMF alone. However, EMF in combination with growth factors (FGF-2 and IGF-I) caused changes in the collagen production in bovine nasal chondrocytes. PEMF in combination with FGF-2 reversed the inhibitory effects of the growth factor on collagen synthesis and slightly increased type II collagen expression (Figure 3a, b). Furthermore, PEMF intensified the stimulatory effects of IGF-I on aggrecan synthesis. However, it significantly inhibited aggrecan expression in combination with FGF-2 (Figure 3c). The stimulatory effect of combined PEMF and IGF-I applications on aggrecan synthesis observed in this study is in agreement with the results of previous studies (2, 32). Our findings regarding combined FGF-2 and EMF applications are in agreement with those of Chang et al. (4) who suggested that chondrocytes somehow terminate the synthesis and deposition of ECM proteins while proliferating.

The EMF effect on RARβ and TGF-β expressions was further explored. RARs have been shown to act as transcription factors and play important roles in chondrogenesis by several groups (12, 13, 16). Kafienah et al. (15) have highlighted the importance of these receptors in chondrogenesis using antagonists against these receptors. They have reported that RA receptors are expressed differentially during chondrocyte maturation and that RARβ is downregulated during chondrogenesis induced by TGF-β (13). Furthermore, they have reported that RARβ expression is negatively correlated with COL2, aggrecan, and SOX9 productions in TGF-β-treated 3D chondrocyte cultures (13). On the other hand, Diederich et al. (12) have reported that RARβ expression is induced by TGF-β in human chondrogenic stem cell pellet cultures, suggesting RARβ to be a good target in studies related to chondrogenesis. However, Zhang et al. (14) have explored the interactions of RA and TGF-β signaling during chondrogenesis and reported a negative functional interplay between RA and TGF-β during chondrogenesis in mouse embryonic palate mesenchymal cells, which in agreement with the findings of Kafienah et al. (15). These discrepancies in the effects of TGF-β on RARβ expressions reported by different research groups are possibly related to the chosen culture conditions, namely 2D (monolayer) or 3D (pellet- or scaffold-based) systems. To test whether EMF has any effect on RARβ and TGF-β expressions, the mRNA levels of RARβ and TGF-β in our culture conditions were measured. We hypothesized that RARβ expression need not be changed or downregulated if the chondrocytes maintain their chondrogenic phenotype with EMF treatment. Both CEMF and PEMF treatments alone or in combination with IGF, but not with FGF-2, downregulated RARβ expression in chondrocytes. CEMF upregulated RARβ expression in combination with FGF-2 (Figure 4). No significant changes were observed in TGF-β expression levels in comparison with the controls. In cell cultures where RARβ expression was upregulated, in agreement with the findings of Kafienah et al. (15), down-regulation was observed in type II collagen and aggrecan expression levels of chondrocytes (Figure 3b, c). Both PEMF and CEMF alone downregulated RARβ expression and caused a slight increase in type II collagen expression (Figure 3b). In our study, induced chondrocyte proliferation with combined EMF and FGF-2 application and increased RARβ expression may be due to the dedifferentiation of rapidly proliferating chondrocytes. RARα expression was not affected by any treatment (data not shown).

Only few studies in the literature have discussed the effects of both PEMF and CEMF on various cells (21, 33). Stolfa et al. (21) have reported that a static magnetic field is more appropriate than PEMF for the stimulation of the metabolic activity of chondrocytes, but in our study, we did not find any difference between the effects of CEMF and PEMF exposure to chondrocytes. Furthermore, it has been suggested that CEMF exposure may induce adaptive mechanisms in cells, protecting the genome from harmful influences, whereas PEMF exposure results in the formation of DNA breaks (34). However, another study has shown completely

diverse effects (35). These differences may be directly related to the methodologies, exposure time, frequency, magnetic field intensity, and cell type used in the studies.

Our study has few limitations. Instead of using 3D cultures (pellet- or scaffold-based), we used monolayer primary chondrocytes that may limit the adaptation and evaluation of the effects of PEMF and CEMF *in vitro* systems with 3D environments. We aimed to overcome this limitation by culturing primary bovine nasal chondrocytes only up to 7 days and analyzing growth factor and matrix protein expressions at this time point.

To our knowledge, this is the first study to analyze CEMF effects on chondrocytes in the presence or absence of growth factors (IGF-I and FGF-2) by means of ECM protein (TGF-β and RARβ) expression. Data reported in the present study, together with previous reports, suggest that EMF exposure may be of interest in cartilage tissue engineering due to its ability to stimulate chondrocyte proliferation and differentiation. Our observations suggest that EMF-mediated chondrocyte proliferation requires the presence of growth factors, especially IGF, in the environment to maintain the chondrogenic phenotype and that EMF effects on chondrocytes are independent of TGF-β and there is no correlation between TGF-β and RARβ expressions.

Ethics Committee Approval: Ethics committee approval was received for this study from Adnan Menderes University Animal Ethics Committee (Approval Date: 24.06.2005, Approval Number: 010-017).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – L.D.K., M.D.B.; Design – L.D.K., M.D.B.; Supervision – L.D.K., M.D.B.; Resource – L.D.K., M.D.B.; Materials – L.D.K., M.D.B., W.K.; Data Collection and/or Processing – L.D.K., M.D.B., A.Ç.; Analysis and/or Interpretation – L.D.K., Ş.G.Ç., A.Ç.; Literature Search – L.D.K., M.D.B., A.Ç., Ş.G.Ç.; Writing – L.D.K., M.D.B., A.Ç., W.K.; Critical Reviews – L.D.K., M.D.B., A.Ç., W.K.

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

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Assessment of the Entrepreneurial Characteristics and Hopelessness Status of Nurses Working in Theonetraining and Research Hospital

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BACKGROUND/AIMS
Due to the vast knowledge they obtain during the education process, nurses become self-confident and successful professionals with a life vision,open to risk taking and change.

MATERIALS and METHODS
The aim of this study was to determine the entrepreneurial characteristics of the nurses, as well as their opinions and the hope or hopelessness status. This research included 140 nurses working in the Training and Research Hospital. The research wasdescriptive and in the screening model. The Beck hopelessness scale (BHS) and the entrepreneurship scale (ES) were utilized as the data collection tools.To determine the hypothesis tests to be used in the comparison of entrepreneurial tendencies of nurses by their indentifying characteristics and the Beckhopelessness scale, the compliance of the dataset with the normal distribution was tested using the Kolmogrov–Smirnov test, and as a result of the test, the scores from both the scales were found to be compliant with the normal distribution. The Levene test was performed to test the homogeneity of variances, which were then identified as homogenous. Therefore, parametric hypothesis tests were used in the research.

RESULTS
In the comparison of entrepreneurial tendencies of nurses consideringthe identifier characteristics and Beckhopelessness scores, the t-test was usedwhen the number of categories in the independent variance was 2, and the variance analysis was performed when it was >2. In addition, the correlations between the entrepreneurial tendencies and Beckhopelessness scores were tested with the Pearson correlation analysis.

CONCLUSION
Therefore, with the increase in the scores obtained by the nurses from the Beck hopelessness scale in the sub-dimension of feelings about future, the scores from the sub-dimensions of self-confidence, innovation, need to accomplish, locus of control and taking risks under the entrepreneurship scale also increase. The nurses with higher levels of hope are self-confident, have higher levels to take risks with more need to accomplish.

Keywords: Creativity, entrepreneur, entrepreneurship, hope, hopelessness

INTRODUCTION

Upon new circumstances forcing the change in increasingly difficult environmental conditions, the effort to create entrepreneurial behaviors such as making investment, changing the work environment, creativity, decisionmaking, and risk taking is a crucial mission in the development of modern societies. The confidence, courage, power to take risks, desire to start one'sown business, taking chances, aim-oriented living, and determinedness generated in the lives of individuals that exist within the personalities would encourage individuals to take entrepreneurship.

Entrepreneurship

Entrepreneurship is the concept that covers risk taking, using opportunities, realization of chancestaken,and making changes (1, 2).

In a study conducted on the subject,a professional entrepreneur was definedas a person with a global mind, who makes decisions with consensus and execute such decisions through a business plan. The concept of entrepreneurship is the

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process where some resources and processes are researched and utilized using chances (3-5).

Studies on the importance of establishing an entrepreneurial culture that will promote entrepreneurship in the organization will lead to entrepreneurial orientation of the individuals because of the dynamism, which is resourcebased andin the world market conditions, producingsuccessful and innovative products for along-term business success. It is important to create this culture in every workplace (6-8).

The most important factor that non-innovation organizations should know is that there is a danger of losing their organizational effectiveness. For this reason, organizations should find and persuade high entrepreneurship-oriented individuals to produce valuable and rare products and services considered to be asustainable competitive advantage and source and to create the added value. It can beseen that there is a move toward creating an environment that supports innovative, proactive, and risk-taking strategic behaviors within the organization (9).

In many studies, increasing the tendency toward entrepreneurship to create innovation and value plays a key role. These studiesemphasized that the most important strategy in competitiveness would be to address innovation, proactivity, and risk-taking dimensions (10-13).

Engelen (14) in their study took into account the cultural dimensions of Hofstede, and entrepreneurship behaviors were examined. The authorsfound that individualism and uncertainty avoidance culture dimensions wereeffective (14).

Özdevecioğlu and Cingöz (15) define the concept of entrepreneurshipas the process in which certain resources and processes are explored and exploited to make good use of certain opportunities. According to İrmiş and Özdemir (16), the entrepreneurship is a processemployedto effectively realize the risk management to identify the work opportunities and use them accordingly and to establish values through the use of management skills. In the formation of values, establishing a profit-oriented new entity, expanding such entity and generating income through the creation of a new good or service defines the entrepreneurship (17).

The internal instinct to be successful might be considered as one of the fundamental tools in increasing the motivation to succeed. When people are successful, they feel more satisfied andhappier. Such people with high desire to be successful do not like routine, and they show effort to create change and new ideas (18). According to Küçük, the individuals with a high-achievement motive have the skills to transform their surrounding into business ideas due to their skills to conductresearch, see details, show interest towardchange, and have the ability to see what the others cannot (19). The entrepreneur is defined as anindependent person who wants to make his or her own decisions, be free, and fulfill his or herdreams (20). Pursuant to Yılmaz (21) and Sümbül, the entrepreneursarevisionary people interested into adopting changes, having the skill to use opportunities, and working towardreaching their future objectives.

The Entrepreneur Nurse

International Council of Nurses (ICN)

In 2004, providedthe definition of the entrepreneur nurse as "nurse control of practice and patient care" as the most significant definition among the others in the literature, and it highlighted that the entrepreneur nurses may also provide services in marketing, public,and the private sector.On the basis of nursing, entrepreneurship is considered as the development, assessment, and sale of healthcare products and devices, legal services, health care/policy consultancy, and health care/policy publications (22). Considering that entrepreneurship isgenerally perceived as the person who produces a product or provides a service and then market thoseto other businesses,the nurse entrepreneur may be seenas the person who establishes and organizes his or her own business as indicated by (3, 23). In terms of the health care, the entrepreneurship may be used as the social change and the change in the provision andorganizationof nursing services. The nurse entrepreneurs are innovative people, who use their creativity to develop new methodsandproduce new ideas, services, or products, or new methods to use the existing products in a different way. They may charge for such service and product and may market a new product to improve the patient care (3-24). The innovativeness had become important by the end of the 1970s and beginning of the 1980s. Davyhoff and Moore defined the innovative person as "intrapreneur"(3) and described the innovative in the health care domain as an entrepreneur working in an existing institution or a system such asa hospital, while the innovativeness isthe main factor in the survival of a health care organization. The profession of nursing contributes to the protection, development, and improvement of health and also reflects the knowledge, skills, and trust to merge the medical administration. Regardless of the cooperation and challenges of the independent practice, the autonomy of the entrepreneurial acts brings momentum to such merging (25-27).

By the end of 2000s, the nurses began to practice in accordance with the entrepreneurship model and created innovative initiatives. The rapid changes in the health care sector and public demand for cheap and quality care introduced autonomous working opportunities to nurses as trainers and consultants (26-28). Particularly, with the increasing significance of nurses in the home care services, the nurses began to show up their individual skills, knowledge, and initiative. Fullbrook indicated that the preliminary condition of professionalism is to walk away from the routine and make aneffort to undertake the duties with creative power and perform them accordingly (29). Kalischuk and Thorpe claimed that creativity enhances the problem solving in the nursing practice (30). Dayyhoff and White noted that the benefits of beinganentrepreneur are reflected in time provided that the work's maturity and becoming a market position (4-28). The period to see the accomplishment of an entrepreneurial operationmay take between 3 and 10 years.

Roles of Nurse Entrepreneurs and Challenges in Their Service Domains

The nurse entrepreneurs provide services in various dimensions as the owners and managers of consultancy activities, education companies, home care agencies, care facilities for adults, child care centers, public clinics, durable medical equipment companies, printing/publication companies,and companies

producing health care products (26). However, complicated legal conditions required to perform new medical planning, lack of professional assistance for private nursing practices, and attitudes of other health care professionals about the special practices in nursing aresome ofthe challenges (31, 32). The concepts of nursing and business are not combined,and while the performance is enhancedin corporate spaces, the performance in other areas isconsidered to deteriorate. The ethical conflicts between nursing and business are underlined (21-23). Legal shortcomings, concerns, and lack of knowledge are also considered as an obstacle in the entrepreneurship activities. The lack of knowledge regarding the law, regulations, and compensation procedures and the general concerns regarding the arrangements cause the loss of entrepreneurship opportunities among nurses. As much as the legal issues, much smooth issues such aslack of intention to struggle with the employers and doctors also lead to the obstacles for entrepreneurship (31, 33-35). That we used their scales upon getting consent, had conducted a study on the senior class students of Kafkas University and Kırıkkale University where they considered the students as a potential entrepreneur and aimed to identify the tendencies of students toward the entrepreneurship (36). For this study, self-confidence, change, need to accomplish, locus of control, risktaking, and tolerance toward the uncertainty were selected as the entrepreneurial characteristics. Considering these findings, students in Kars and Kırıkkale were found thatthey performedtheentrepreneurial activities at a significant level,hadthe potential to establish a business, and had business ideas. The study also indicated that although the students had self-confidence, the tendency tochange, needed accomplishment, had locus of control, and the tendency to take risks, yet they did not show any tolerance toward uncertainty.

The Status of Hopelessness Perception

When the entrepreneurial characteristics are evaluated, emotions should be considered as well. The negative feelingsabout the futureof individuals have a negative impact on the coping methods with the problems and the adaptation process to their surroundings (37). Hope is definedas "an expectation greater than zero,"and hopelessness is "an expectation less than zero in the realization of an aim, in brief no expectations" (38). Considering the cognitive theory of Beck, hopelessness is considered to bethe basis of depression (39), and hope isan emotional element of the expectation to reach an aim (40). The concept of hope is defined asanemotion, expectation, illusion, and desire, and it was stated that hope facilitates the potentials of individuals through protecting them and isan instinctive component of life. As the opposite of hope, hopelessness is expressed as the negative expectationsregardingfuture and is an obstacle (41). The things to be done by individuals and their contributions to their surroundings increase parallel to the positivity level of their thinking and decrease parallel to their hopelessness level (42). Anincrease in the hopelessness level has an opposite impact on the problem-solving abilities, productivity, and success of an individual compared to hope. While hope is argued to be a feature that injects the feeling of wellness and motivates the person to stand up (43), it is defined as the anticipation to accomplish beliefs and plans to find an exit, in addition to positive developments (44). Hopelessnessis expressed in the way that the individual defines oneself with the negative features andnegative expectations aboutthe future and the belief that negativity would stay (45, 46). The feeling of hopelessness is closely related tothe cognitive nature and information-processing style of individuals (47, 48), meaning that the individuals who assignwrong meanings to their experience regardless of theobjective or thereal reason expect negative outcomes without even showing any effort to accomplishthose objectives,andthedevelop negative expectations aboutfuture as an outcome (49-51).

Study Aim

The aim ofthis study was to evaluate entrepreneurial features of nurses working at the Near East University Training and Research Hospital and their perceptions regarding hope and hopelessness together. In addition, this study also aimed to identify the entrepreneurial features of nurses working at the Near East University Training and Research Hospital andthe impact of such features on theirsfeeling of hope and hopelessness, based on the scientific foundations, andto furthercontribute to the relevant literature. The questions leading thisevaluation in terms of various variables were the following:

Is there any variance in the entrepreneurship views of nurses' inconsideration with their professional experience?

Is there any variance in the views of nurses about entrepreneurship?

Is there any variance in the views of nurses about experiencing hopelessness?

MATERIALS and METHODS

This section explainsthe model, population, sample, data collection tools, statistical method, and techniques in data collection and data analysis.

Research Model

The screening model as one of the descriptive research methods was utilized to identify the entrepreneurial tendencies and hopelessness levels innurses."In a multiple-component population, the screening model is the screening arrangements conducted on the whole population or a group, example, or sample of that population to reach a general fact"(52).

Population and Sample

In this study, a population of 140 nurses working at the hospital located in Turkish Republic of Northern Cyprus for the academic year of 2015–2016 was included. Among the nurses, 86.52% were women, and 13.48% weremen. 42.70% of nurses were aged ≤24 years, 26.97% were 25–26 years,and 30.34% were ≥27 years. Considering education, 15.73% nurses graduated from a vocational high school or had a 2-year degree, while 84.27% hada bachelor's degree orcompleted apost-graduate program. 38.51% of nurses had a professional experience for ≤1 year, 26.97% had 2 years, 11.24% had 3 years, and 29.21% had ≥4 yearsof experience. 59.55% of nurses had a previous entrepreneurshipexperience. Within the scope of this research, 39.33% of nurses had a business idea.

Data Collection Tools

As a data collection tool of this research, we used a questionnaire with three sections:identifier features, the Entrepreneurship scale (ES), and Beck hopelessness (BHS) inventory.

The first section of questionnaire included introductory questions prepared by the researcher aboutthe details such as gender, age, and type of completedhigh school.

To identify the entrepreneurial tendencies of nurses included in the research, the entrepreneurship scale developed by İşcan and Kaygın (36) in 2011 was utilized under the second section of questionnaire. The scale was developed as a 5-point Likertscale with 28 items. The validity and reliability process was performed by İşcan and Kaygın on the total number of sixsub-dimensions of the scale as self-confidence, change, need to accomplish, locus of control, risk taking, and tolerance toward the uncertainty, with atotal variance of 51.75%. The Cronbach alpha values of sub-dimensions varied between 0.61 and 0.79. As a result of the reliability analysis conducted by the researcher in relation tothe scale, the Cronbach alpha values were found to range between 0.76 and 0.85. Considering such results, the entrepreneurship scale was considered as a valid and reliable scale in the identification of entrepreneurial tendencies of nurses included in the third section of questionnaire, the original Beck hopelessness scale was developed by Beck in 1963 andtranslated andadapted into Turkish by Seber et al. in 1993 (53). The scale is comprised of propositions with 11 right and 9 wrong keys. Each proposition in compliance with the key is given 1 point, while each incompliant proposition gets 0 points. The average score of participants from the scale was calculated as the hopelessness score. The propositions of the 1st, 6th, 13th, 15th, 19th were related with the feelings about future; the 2nd, 3rd, 9th, 11th, 12th, 16th, 17th, 20th with the loss of motivation; and the 4th, 7th, 8th, 14th, 18th expectations from the future.

Following the development of questionnaire as the data collection tool, the Near East University Ethics Board was referred for an authorization to administerthe questionnaire tonurses within the scope of population. After the authorization, the questionnaire was administered in the form of aninterview in April 2016. To ensure sincere and correct responses from the participants, the nurses were informed aboutthe significance of research, confidentiality that they did not need to write their names on the questionnaire, and that the collected information was to be read onlyby the researcher.

Data Analysis

The data collected from the questionnaire were entered intothe electronic environment and analyzedwith the Statistical Package for the Social Sciences version 21,0 statistics program (SPSS IBM Corp.; Armonk, NY, USA). Primarily, the distribution of the responses for the identifier features, entrepreneurship, and Beckhopelessness scale was determined through the frequency analysis, and the descriptive statistics regarding the scores from the sub-dimensions of scales were calculated. To identify the hypothesis tests to be used to compare the entrepreneurial tendencies in terms of identifier features and scores from the Beck hopelessness scale, the compliance of dataset with the normal distribution was tested using the Kolmogrov–Smirnov test, and the scores of nurses forboth the scales were identified as in compliance with the normal distribution. Therefore, parametric hypothesis tests were used in the research. In the comparison of entrepreneurial tendencies of nurses with the identifier characteristics and Beck hopelessness scores, the t-test was conducted when the number of categories in the independent variance was 2, and the variance analysis was performed when it was >2. In addition, the correlation between the entrepreneurial tendencies and Beckhopelessness scores was tested usingthe Pearson correlation analysis. The findings section discussed the entrepreneurial tendencies and Beck hopelessness scores of nurses, their entrepreneurial tendencies by their identifier features and variances between the Beck hopelessness scores, and the relationship between the entrepreneurial tendencies and Beck hopelessness scores.

Considering Table 1, the average score of nurses from the entrepreneurship scale in general was found as 59.89±13.94 with the lowest score of 28 and the highest of 139. The nurses obtained 7.19±2.37 as an average from the self-confidence sub-dimension, 12.33±3.79 from change sub-dimension, 10.90±3.44 from the need to accomplish, 12.22±3.66 from locus of control, and 6.65±2.32 from the tolerance of uncertainty. The nurses had an average of 5.71±4.02 from the Beck hopelessness scale with the lowest score of 0 and highest of 24. In relation with the Beck hopelessness scale, the average score for the future feelings was 0.84±1.26, 2.91±2.29 from loss of motivation, and 1.96±1.36 from future expectations.

When Table 2 was evaluated, comparing the work experiences of nurses and the scores from the entrepreneurship scale, there was no statistical variance between the scores obtained from the sub-dimensions of self-confidence, change, locus of control, and tolerance toward uncertainty ($p<0.05$). Regardless of their work life, the nurses obtained similar scores from these sub-dimensions. The variance between the scores from the sub-dimension of need to accomplish in terms of their work life was found to besignificant ($p<0.05$). Such variance was found for nurses working for 3 years, who obtained lower scores from the need to accomplishment sub-dimension. Among who participated in this study, there wasa statistically significant variance between the scores from the entrepreneurship scale ($p<0.05$). The scores fornurses from the sub-dimension of risk taking were identified as statistically significant ($p<0.05$). The nurses with ≤1 year, and 3-year work experience obtained lower statistically significant scores than the nurses with 2- and 4-year work ex-

TABLE 1. Descriptive statistics for the scores of nurses fromt he entrepreneurship scale and the Beck hopelessness scale

ScScales and Sub-dimensions	n	x̄	s	Min.	Max.
G Entrepreneurship scale	89	59.9	13.94	28	139
Nurses obtained	89	7.19	2.37	4	20
Innovation	89	12.33	3.79	6	30
Successneeds	89	10.90	3.44	5	25
Locus of control	89	12.22	3.66	6	30
Risk taking	89	1110.60	3,13.13	5	2525
Tolerance to uncertainty	89	6.65	2.32	2	10
BBeck hopelessness scale	89	5.71	4.02	0	24
AThe agree score for the future	89	0.84	1.26	0	5
MMotivation	89	2.91	2.29	0	12
FFuture expectations	89	1.96	1.36	0	7
BBeck hopelessness scale totals	89	5.71	4.02	0	24

TABLE 2. Comparison of scores obtained by the nurses in terms of their work experience

	Working time	n	x̄	s	Min.	Max.	F	p
Confidence	I year and below	29	7.10	2.37	4	14	1.34	0.27
	2 year	24	7.96	2.73	4	12		
	3 year	10	6.50	2.12	4	10		
	4 years and below	26	6.85	2.03	4	10		
Innovation	I year and below	29	12.14	3.68	6	23	2.63	0.06
	2 year	24	14.04	4.12	7	21		
	3 year	10	11.40	3.50	6	16		
	4 years and below	26	11.31	3.31	6	17		
Success needs	I year and below	29	10.24	3.33	5	19	4.04	0.01*
	2 year	24	12.04	2.31	8	16		
	3 year	10	8.20	3.29	5	15		
	4 years and below	26	11.62	3.90	5	20		
Locus of control	I year and below	29	11.07	2,81	6	18	2.59	0.06
	2 year	24	12.,88	3.66	6	20		
	3 year	10	11.00	3.65	6	15		
	4 years and below	26	13.38	4.16	6	20		
Taking risk	I year and below	29	9.52	2,95	5	17	3.50	0.02*
	2 year	24	11.38	2.81	5	17		
	3 year	10	9.20	2.74	5	13		
	4 years and below	26	11.62	3.31	5	19		
Tolerance to uncertainty	I year and below	29	6.21	2.65	2	10	2.22	0.09
	2 year	24	6.33	1.99	3	10		
	3 year	10	6.20	2.30	3	9		
	4 years and below	26	7.62	2.02	2	10		
Entrepreneurship scalestotals	I year and below	29	56.28	13.23	31	98	2.98	0.04*
	2 year	24	64,63	12,91	41	84		
	3 year	10	52.50	14.65	29	77		
	4 years and below	26	62.38	13.87	28	84		

*p<0.05

perience. Considering the results, the nurses with ≥4 years of-work experience are most willing to takerisks. The nurses with a longerwork experience take more risks. There was a statistically significant variance between the scores obtained from the entrepreneurship scale in general (p<0.05). Considering Pearson's correlation analysis to determine the correlation between the scores obtained by nurses from the sub-dimensions of Beck hopelessness scale and sub-dimension of the entrepreneurship scale as presented in Table 3, a statistically significant correlation between the scores under the sub-dimension of feelings about future within the Beck hopelessness scaleandthesub-dimensions of self-confidence, innovation, need to accomplish, locus of control, and taking risks within the entrepreneurship scale was identified (p<0.05). Such correlations were positive and weak. Therefore, with anincrease in the scores obtained from the Beck hopelessness scale in the sub-dimension of feelings about future, the scores from the sub-dimensions of self-confidence, innovation, need to accomplish, locus of control, and risk taking under the entrepreneurship scale also increase. Thus, it might be interpreted thatnurses with a higher level of hope are self-confidentand are more prone to risk taking,with more need to accomplish. Nurses withahigher level of hope are more self-confident and open to change.

RESULTS

The studies havefocused on the fact that the entrepreneurial potential must exist for entrepreneurship to emerge. This section discussesthe entrepreneurial tendencies and Beck hopelessness scores of nurses, their entrepreneurial tendencies by their identifier features, and variances between the Beckhopelessness scores, and the relations between the entrepreneurial tendencies and Beckhopelessness scores (Table I).

According to Table I, the average score of nurses from the entrepreneurship scale in general was found as 59.89±13.94 with the lowest score of 28 and highest of 139. The nurses obtained 7.19±2.37 as an average from the self-confidence sub-dimension, 12.33±3.79 from change sub-dimension, 10.90±3.44 from the need to accomplish, 12.22±3.66 from locus of control, and 6.65±2.32 from the tolerance toward the uncertainty. The nurses got an

TABLE 3. Correlations between the scores of Beck hopelessness scale and the entrepreneurship scale

Beck Hopelessness Scale/ Entrepreneurship Scale		Confidence	Innovation	Success Needs	Locus of Control	Risk Taking	Tolerance to Uncertainty
Feelings about future	R	0.28	0.38	0.34	0.29	0.31	0.04
	P	0.01*	0.00*	0.00*	0.01*	0.00*	071
Motivation							
loss	r	0.20	0.20	0.08	0.13	0.07	-0.27
	p	0.06	0.06	0.44	0.23	0.51	0. 01
Future							
Expectations	r	0.18	0.15	0.06	0.04	0.07	-0.10
	p	0.10	0.15	0.58	0.72	0.53	0.37

*p<0.05

average of 5.71±4.02 from the Beck hopelessness scale with the lowest score of 0 and highest of 24. Intherelation with the Beck hopelessness scale, the average score for the future feelings was 0.84±1.26, 2.91±2.29 for the loss of motivation, and 1.96±1.36 for future expectations (Table 2).

When Table 2 was evaluated, comparing the work experiences of nurses and the scoresfromthe entrepreneurship scale, there was no statistical variance between the scores obtained from the sub-dimensions of self-confidence, change, locus of control, and tolerance toward uncertainty (p<0.05). Regard less of their work life, the nurses obtained similar scores from these sub-dimensions. The variance between the scores from the sub-dimension of the need to accomplish in terms of their work life was found to be significant (p<0.05). Such variance originated from the nurses working for 3 years, who obtained lower scores from the need to accomplish sub-dimension. In addition, there wasa statistically significant variance found between the scores of nurses from the entrepreneurship scale (p<0.05). The scores of nurses from the sub-dimension of risk taking by the work experience were identified as statistically significant (p<0.05). The nurses with ≤1 year of experience, and 3-year work experience obtained lower statistically significant scores than the nurses with 2- and 4-year work experience (Table 3). Considering Pearson's correlation analysis to determine the correlations between the scores obtained by the nurses from the sub-dimensions of Beck hopelessness scale and the entrepreneurship scale presented in Table 3, a statistically significant correlation between the scores under the sub-dimension of feelings about future within the Beck hopelessness scale and sub-dimensions of self-confidence, innovation, need to accomplish, locus of control, and risk taking within the entrepreneurship scale was identified (p<0.05). Such correlations were positive and weak. Therefore, with anincrease in the scores obtained by the nurses from the Beck hopelessness scale in the sub-dimension of feelings about future, the scores forthe sub-dimensions of self-confidence, innovation, need to accomplish, locus of control, and risk taking from the entrepreneurship scale also increase.

DISCUSSION

International Council of Nurses (ICN)

In 2004, indicated that the definition of entrepreneur nurse as "nurse control of practice and patient care" is the most significant definition among the others in the literature, and it highlighted that the entrepreneur nurses may also provide services in marketing, public, and private sector. The nurse entrepreneur may be definedas the person who establishes and organizes his or her own business as indicated by (3, 23). Such people are innovators, and theyuse their creativity to produce a new idea, services, or products, ortheydevelop new methods to use the existing products in a different way. They charge people in exchange fortheir creativity, service, and products. Development and marketing of a new product for patient care may be given as an example of nurse entrepreneurship (3, 24).

Changes in the health sector demand of the society to access the cost-effective and quality-care-created autonomous work opportunities for the nurses as trainers and consultant (26, 28).

This present study aimedto evaluate the entrepreneurial features of nurses working at the Near East University Training and Research Hospital and their perceptions regarding the feelings pf hope and hopelessness together. In addition, this study also aimedto identify the entrepreneurial features working at the Training and Research Hospital and the impact of such features on their feelings of hope and hopelessnessand to base this on the scientific foundations and contribute to the relevant literature.

The screening model as one of the descriptive research methods was utilized to identify the entrepreneurial tendencies and hopelessness levels of nurses.

A total of 140 nurses working at the hospital located in Nicosia, Turkish Republic of Northern Cyprus for the academic year of 2015–2016 were included into this study. There were 86.52% women and 13.48% men. 42.70% of nurses were aged ≤24 years, 26.97% were 25–26 years, and 30.34% were ≥27 years. Considering education, 15.73% of nurses graduated from a vocational high school or had a 2-year degree, while 84.27% had a bachelor's degree or completed post-graduate program. 38.51% of nurses had a professional experience ≤1 year, 26.97% 2 years, 11.24% 3 years and 29.21% 4 years and above. 59.55% of nurses had a previous experience in entrepreneurship. A total of 39.33% of nurses had a business idea.

These results indicate that themajority of nurses have other business ideas in addition to entrepreneurial initiative, which is considered as positive. As a data collection tool of this re-

search, a questionnaire with three sections (identifier features, entrepreneurship scale, and Beck hopelessness inventory) was applied. The first section of questionnaire included introductory questions prepared by the researcher with regard to gender, age, and level of education.

To identify the entrepreneurial tendencies of nurseswho participated in the research, the entrepreneurship scale developed by İşcan and Kaygın in 2011 was utilized under the second section of the questionnaire. The scale was developed as a 5-point Likert scale with 28 items. The validity and reliability process was performed by İşcan and Kaygın on the total number of sixsub-dimensions of the scale: self-confidence, change, need to accomplish, locus of control, risk taking, and tolerance toward the uncertainty with the total variance of 51.75%. The Cronbach alpha values of sub-dimensions varied between 0.61 and 0.79 (-36). As a result of the reliability analysis conducted by the researcher in relation with the scale, the Cronbach alpha values were found to range between 0.76 and 0.85. Considering such results, the entrepreneurship scale was considered to bevalid and reliable in the identification of entrepreneurial tendencies of nurses. The original Beck hopelessness scale developed by Beck in 1963 was included in the third section and translated and adapted into Turkish by Seber et al. in 1993 (53). The scale is comprised of propositions with 11 right and 9 wrong keys. Each proposition in compliance with the key is given 1 point, while each proposition that is not in compliance is given 0 points. The average score of participants from the scale was calculated as the hopelessness score. The propositions of the 1st, 6th, 13th, 15th, 19th were related with the feelings about future; the 2nd, 3rd, 9th, 11th, 12th, 16th, 17th, 20th with the loss of motivation; and the 4th, 7th, 8th, 14th, 18th with theexpectations from the future. After the authorization from the University Ethics Board, the questionnaire was applied as an interviewin April 2016.

This research included 140 nurses working in the hospital.

Strengthening the entrepreneurial nature of nurses working in the university hospital would make them more successful in the professional life; hence, arelevant training should be planned and implemented.

The efforts toward ensuring much independent nursing profession in the health domain and enhancing the feeling of hope should be increased.

Research opportunities and practice laboratories that would speed up the studies of nurses with entrepreneurial potential should be provided, and the nurses should be supported in patient care and other professional roles. The results show that the nurses with hopes for the future and open to change have a high potential to succeed should be taken into accountas the nurses with higher levels of hope would benefit theirplace of work.The enhancement of entrepreneurial features of nurses in their field should be increased, and the efforts toward finding new practices with regard to patient care should be endeavored. The experiences of nurses working at the hospital should be taken into consideration, and the efforts should be in place to bring in new practices accordingly.

Considering the experience of nurses working in the hospital, efforts should be made to find new practices by consideringtheir opinions on patient care and treatment, and setting up an environment.

In the increasingly competitive conditions in the world, the amount of support for entrepreneurial nurses should be increasedas well.

It is necessary to plan and conduct teaching that will improve entrepreneurship and perspective of innovations through in-service programs for newly recruited nurses. Extending and updating content in terms of innovation and creativity will help to increase the effectiveness of programs.

Ethics Committee Approval: Ethics committee approval was received for this study from Near east University (Approval Date: 05.11.2015, Approval Number: 239).

Informed Consent: All participants received written and oral information on all aspects of the study and gave written consent to participation.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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Minimal Invasive Surgery in Newborns and Infants: Northern Cyprus Experience

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BACKGROUND/AIMS
Pediatric minimal invasive surgery (MIS) is a relatively recent approach in Northern Cyprus, where it is being performed for less than a decade. This is the first study reflecting our initial experience with MIS in newborns and infants.

MATERIAL and METHODS
The case records of all laparoscopic and thoracoscopic procedures performed on children younger than 1 year by two pediatric surgeons at two different hospitals (university hospital and state hospital) during 2012–2017 were collected and retrospectively analyzed. Statistical analysis was performed using SPSS version 22 for Macintosh. The descriptive statistics are presented as frequencies, percentages, and means. To determine the relationship between principal variables and other continuous variables, Pearson correlation test was used. A p-value of <0.05 was considered statistically significant.

RESULTS
The hospital records of 18 patients [15 (83.3%) boys and 3 (16.7%) girls] were included in the study. The mean age at the time of procedure was 5 months 10 days (1 day–11 months). The surgical procedure was gastrointestinal in 9 (50%), urologic in 5 (28%), gynecologic in 2 (11%), and thoracic in 2 (11%) cases. The mean operative time was 74 (15–355) min. The operative time and hospitalization time both showed a tendency to increase in patients who were younger, but these findings were not statistically significant. Postoperative feeding was started at a mean 1.9 (range, 0–7) days. The feeding resumption time was significantly correlated with age (p=0.03). The mean postoperative hospitalization time was 8.7 (range, 0–32) days and the median was 2 days.

CONCLUSION
The initial experience from our patients shows results similar to those reported in the literature that MIS in infants is a safe and efficient option, even in low-populated countries, as long as the procedure is performed by pediatric surgeons who have completed their learning at high-volume centers.

Keywords: Infants, laparoscopy, minimal invasive surgery, pediatric surgery

INTRODUCTION

Minimal invasive surgery (MIS) refers to the procedures performed with a minimal incision or through a natural orifice using trocars, telescopes, insufflation, and specialized instruments (1). Although the initial experience with MIS in children has been reported as early as the 1970s, the real momentum started after wide adaption of this approach by pediatric surgeons in 1990s (2-4). Many pediatric procedures have been performed with favorable outcomes since then. MIS offers excellent cosmetic appearance, which is crucial in pediatric cases where incision scars have a risk of growing and deforming with age. Moreover, better functional results due to a decreased risk for intraabdominal adhesions, postoperative wound dehiscence, infection, herniation, decreased postoperative pain, and length of hospital stay mark the importance of MIS in pediatric population (5-10). However, besides these advantages, MIS is associated with the difficulty of working in a small area, limited freedom of surgeon's hand movement, and attempt to perform the entire surgery with straight and nonrotating instruments. Some of these difficulties have recently been eliminated by robotic surgery. Nonetheless, specialized training is needed to perform MIS, and it has a steeper learning curve than open surgeries.

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Pediatric MIS is a relatively recent approach in Northern Cyprus, where it is being performed for less than a decade. This is the first study reflecting our initial experience with MIS in newborns and infants.

MATERIAL and METHODS

The study was approved by the Institutional Near East University Ethical Committee (Approval Date: 22.02.2018, Approval Number: YDU/2018/55-535).The case records of all laparoscopic and thoracoscopic procedures performed on children younger than 1 year by two pediatric surgeons at two different hospitals (university hospital and state hospital) during 2012–2017 were collected and retrospectively analyzed. Both pediatric surgeons had completed their MIS training at high-volume centers abroad. The cases with missing or incomplete hospital records were excluded from the study population. All surgical procedures were performed after obtaining written informed consent from the parents.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 22 for Macintosh (SPSS IBM Corp.; Armonk, NY, USA). The descriptive statistics are presented as frequencies, percentages, and means. To determine the relationship between principal variables and other continuous variables, Pearson correlation test was used. A p-value of <0.05 was considered statistically significant.

RESULTS

The hospital records of 18 patients [15 (83.3%) boys and 3 (16.7%) girls] were included in the study. The mean age at the time of the procedure was 5 months 10 days (1 day–11 months). The surgical procedure was gastrointestinal in 9 (50%), urologic in 5 (28%), gynecologic in 2 (11%), and thoracic in 2 (11%) cases. The indications for surgery are listed in Table 1. The most frequent indication for MIS in our study population was nonpalpable testis (4 patients, 22.2%). Furthermore, the two most frequent MISs performed in our study group were diagnostic laparoscopy (4 patients, 22.2%) and gastrostomy placement (3 patients, 16.5%) (Table 2). Of the 4 patients undergoing diagnostic laparoscopy, 3 were those with a nonpalpable testis. Among the 4 patients with a nonpalpable testis, 3 had a vanishing testis, and excision of the nubbin was performed for them; the remaining 1 patient had intraabdominal testis, and single-stage laparoscopic orchidopexy was performed for this patient. Laparoscopic gastrostomy placement was performed in 2 patients with oral feeding difficulties due to neurological impairment and 1 patient with isolated esophageal atresia. The mean operative time was 74 (15–355) min. There were 2 unintended conversions to open surgery. One was due to hemodynamic instability and ventilation difficulty during thoracoscopic diaphragmatic repair, and the other was a failed laparoscopic reduction attempt at intussusception. Postoperative complication developed in only patient in our study group; it included early postoperative collection and wound dehiscence in the 3-mm port incision site. This condition resolved spontaneously with conservative management. No obvious bleeding incident occurred during surgery in all patients. Excluding 1 patient who was hospitalized for 6 months due to conditions unrelated to laparoscopy, the mean postoperative hospitalization time was 8.7 (range, 0–32) days and the median was 2 days. The operative time and hospitalization time both showed a tendency to increase in patients who were younger, but these findings were not statistically significant. Postoperative feeding was started at a mean 1.9 (range, 0–7) days. The feeding resumption time was significantly correlated with age (p=0.03).

DISCUSSION

Today, in the era of MIS, pediatric laparoscopy has become widely popular. Pediatric MIS is being utilized in many centers worldwide as a primary approach for abdominal and thoracic surgical pathologies. The momentum gained by MIS in mid-1990s has led the pediatric surgery community to research and develop novel techniques for known problems. The application of MIS in neonates and infants dates from the late 1990s and has come a long way since then (7, 11-14). Surgical procedures in small children, infants, and neonates require additional skills from both surgical and anesthesia teams. First, the surgeon has to work in a smaller cavity; this complicates the approach, especially in complex procedures requiring intracorporeal suturing. At the same time, prolonged operative time and surgeon fatigue increase the risk for inadvertent tissue and organ injuries. The anesthetic management in these cases poses special problems due to the pneumoperitoneum created and extremes of position adopted in addition to the fact that pediatric anesthesia itself is a challenge. Mostly the physiological

TABLE 1. Indications for minimal invasive surgery

Surgical indication	n	(%)
Adnexal torsion	2	11.1
Oral feeding difficulties	2	11.1
Congenital diaphragmatic hernia	2	11.1
Hirschsprung disease	2	11.1
Intestinal obstruction	1	5.6
Intussusception	2	11.1
Esophageal atresia	1	5.6
Cholelithiasis	1	5.6
Ureteropelvic junction obstruction	1	5.6
Nonpalpable testis	4	22.2
Total	18	100

TABLE 2. Surgical procedures

Surgical indication	n	(%)
Diagnostic laparoscopy	4	22.2
Gastrostomy placement	3	16.5
Thoracoscopic diaphragmatic hernia repair attempt	2	11.1
Adnexal cystic mass removal	2	11.1
Intussusception reduction attempt	2	11.1
Cholecystectomy	1	5.6
Laparoscopy-assisted transanal endorectal pull-through	1	5.6
Ladd procedure and extramucosal intestinal biopsy	1	5.6
Orchidopexy	1	5.6
Anderson–Hynes pyeloplasty	1	5.6
Total	18	100

and anesthetic considerations are the same, except that child is not a small adult (15). As for the anesthesia team, the smaller abdominal volume may predispose the patient to ventilation difficulties during gas insufflation. Moreover, pressure changes across the gas container, insufflator, and patient's thorax/abdomen cause cooling due to the Jewel–Thompson effect; this issue is especially important in neonates, who are prone to hypothermia.

Minimal invasive surgery should be performed by experienced surgeons at dedicated centers; the training itself requires a steeper learning curve than open surgery. MIS does not always imply minimal harm to the patient. Prolonged operation room stay, prolonged exposure to anesthesia, and inadvertent damage to the adjacent structures are only some of the risks that patients face in the inexperienced hands. A study by Oomen et al. (16) has shown that surgical complications decrease dramatically from 31.5% to 11.4% after the first 35 laparoscopic pyloromyotomies performed during the learning curve. Cusick et al. (17) have shown that the learning curve for laparoscopic splenectomy reaches a plateau after the initial 20 cases. The evidence from the literature highlights the importance of working and training at high-volume centers, and this is probably the most important challenge that surgeons in low-populated areas have to overcome.

A laparoscopic approach offers several advantages over open procedures: 1) it potentially reduces the surgical stress and fluid shifts that may accompany it; 2) it is associated with a less need for postoperative analgesia and with reduced postoperative respiratory and wound complications; 3) it shortens postoperative convalescence, including the intensive care unit stay; and 4) it is associated with a rapid return to normal diet and with a decreased overall hospital stay (18). Although being quite recent, the results in our series show favorable outcomes regarding intraoperative and postoperative complications associated with MIS. Only 1 patient (5.6%) developed a minor wound complication, which resolved with conservative management. Two patients needed conversion to open surgery. Feeding resumption in our group was significantly correlated with age, with a shorter feeding resumption time observed in older babies. The reason for this correlation was that the surgery performed in these patients mostly comprised diagnostic laparoscopy and urologic procedures. The mean feeding resumption time observed in this study seems long (8.7 days), but due to the variability of the procedures in this series, we prefer to accept the median feeding resumption time of 2 days. Although statistically insignificant, hospitalization time observed in this study also showed a tendency to increase with a younger age; this was again related to the complexity of the procedures performed in smaller children. The operative time also varied greatly (74±89 min) due to the diversity of the cases within the study group. Overall, the initial experience from our patients shows results similar to those reported in the literature that MIS in infants is a safe and efficient option, even in low-populated countries, as long as it is performed by pediatric surgeons who have completed their learning at high-volume centers. The pediatric surgeons who work in these regions should use the opportunities to follow the innovations and continue their education. They should safely and effectively use MIS in children, as it is widely used across the world and has become the gold standard for most of the surgeries.

Ethics Committee Approval: Ethics committee approval was received for this study from Near East University Ethics Committee (Approval Date: 22.02.2018, Approval Number: YDU/2018/55-535).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – E.K, G.K; Design - E.K, G.K.; Supervision - E.K, G.K.; Resource - E.K, G.K.; Materials - E.K, G.K; Data Collection and/or Processing - E.K, G.K; Analysis and/or Interpretation - E.K, G.K; Literature Search - E.K, G.K; Writing - E.K, G.K.; Critical Reviews - E.K, G.K.

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

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

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The Knowledge Level of Hospital Staff about Influenza and Pneumococcal Vaccination

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BACKGROUND/AIMS
The aim of this study was to evaluate the knowledge of health care workers (HCW) on the influenza and pneumococcal vaccine.

MATERIALS and METHODS
A questionnaire about influenza and pneumococcal vaccination was administered to HCW and administrative staff.

RESULTS
A total of 225 subjects were included into the study; there were 180 women (80%) and 45 (20%) men. The mean age was 31.9±11.4 years, and 73.5% of the respondents stated that adult vaccination was effective. Pneumococcal vaccination (58.7%) was less well known, although 86.2% of respondents indicated that they were familiar with influenza vaccination. Only 28.4% of respondents indicated that they had influenza vaccine, and none of the cases had a pneumococcal vaccine. In 75% of influenza-vaccinated participants, the vaccination was suggested by a physician. Among influenza-vaccinated participants, the percentage of people who thought that vaccination was beneficial was 54.4%. The most common reasons for not vaccinating all participants were the belief that vaccination was ineffective (38.7%) and the belief about not being in a risk group (36.1%).

CONCLUSION
It was shown that the rate of influenza vaccination among hospital staff is low, and most of them were not familiar with pneumococcal vaccination. It is thought that educational programs on vaccination should be made to increase the awareness of the hospital staff who are at risk of infection due to their working environment.

Keywords: Health personnel, influenza vaccines, knowledge, pneumococcal vaccines

INTRODUCTION

Influenza and pneumococcal infections are potential causes of mortality and morbidity for certain high-risk groups, including adults (1). Despite an appropriate treatment, the fatality rates for pneumococcal bacteremia remain high (15%–20%) in some high-risk adults (2). The incidence of pneumococcal diseases varies seasonally with the incidence of flu. Influenza virus damages epithelial cells of airways and improves the condition for secondary bacterial infection (mostly *Streptococcus pneumoniae*) (3). In the United States, during the 2014–2015 flu season, a total of 17,911 patients were hospitalized due to influenza infection with a mortality rate of 9.3% (4).

Influenza and pneumococcal disease control strategies include immunization of high-risk populations (3). Although the efficacy and effectiveness of influenza and pneumococcal vaccines has been proven, the rate of vaccination remains suboptimal worldwide (5).

This study presented as a poster at 21th Annual Congress of Turkish Thoracic Society on 2018 April 1, Antalya, Turkey.

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The Center for Disease Control and Prevention (CDC) in the United States reported that the vaccination coverage for influenza in the 2009/2010 flu season was 41.2% for all ages and 69.6 for those aged ≥64 years (5). Vaccination coverage of pneumococcal infections is lower than that of influenza among high-risk groups globally. According to a survey from Canada in 2006, 39% of adults aged ≥65 years received a pneumococcal vaccine, whereas 70% received influenza vaccine for the same season (6). Health care providers are at high risk of both acquiring and transmitting influenza to patients and other medical staff. It is reported that influenza in health care workers (HCW) can lead to nosocomial outbreaks. Therefore, immunization is recommended for health professionals by the World Health Organization, CDC, and national health authorities of most European countries (7).

The awareness of medical staff about their risk of acquiring influenza and immunization strategies in adults with comorbidities can lead to successful vaccination programs. Consequently, in this study, we aimed to understand the knowledge on influenza and pneumococcal vaccines among HCW.

MATERIALS and METHODS

A comprehensive search was conducted between September and October 2017 in the study. A self-administered questionnaire was performed for all volunteer hospital staff. Hospital staff included HCW and administrative staff. The HCW included nurses, technicians, and laboratories. Approximately 356 hospital staff were contacted, and 225 of them responded to the questionnaire.

The demographic characteristics (age, gender, duration of working) of participants and the results of the questionnaire were recorded. The questionnaire was prepared by specialists in pulmonary disease and infectious diseases, and it was not a validated questionnaire. It included 10 questions about influenza and pneumococcal vaccines. The knowledge of influenza and pneumococcal vaccines, the effect of the vaccines on reducing the infection risk, vaccination rates among hospital staff, and reasons for refusing the vaccine were examined. The knowledge of vaccination was defined according to the following question: "Do you have knowledge about influenza/pneumococcal vaccine?" The answers were classified as yes, no, or no idea. If the participants were sure about the answer, they chose yes or no, but, if they were not sure about the question, they chose "no idea." For example,

- I am familiar with the name of the vaccine, and I know the efficacy. Yes
- I am not familiar with the name of the vaccine, and I do not know the efficacy. No
- I am familiar with the vaccine, but not with its effectiveness. No idea

All participants were informed about the aim of the study, and they gave written informed consent. The study was approved by the local ethical committee of University of Kyrenia (10/18/2018, ref no: RY-2018-11).

Statistical Analysis

Statistical analyses of the study were performed using the IBM Statistical P ackage for the Social Sciences for Windows version 20.0 (SPSS IBM Corp.; Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as counts (percentage). Comparisons of categorical variables between the groups were performed using the chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 225 subjects were included in the study; there were 180 women (80%) and 45 (20%) men. The mean age of the population was 31.9±11.4 years (min, 19; max, 65). The mean age was higher in women than men, and the difference was statistically significant (p=0.001). Nearly 60% of the hospital staff had been working for at least 5 years. The working area and the duration of working of the participants are shown in Figures 1 and 2.

Seventy-tree percent of the respondents stated that adult vaccination was effective. There was no statistically significant difference between genders regarding the opinion on the effectiveness of adult vaccination (women: 72.5%; men: 77.8%; p=0.05). Pneumococcal vaccination (58.7%) was less well known, although 86.2% of respondents indicated that they had information about influenza vaccination (Figure 3). Similarly, the level of knowledge about the effect of the pneumococcal vaccine on the reducing risk of infection (40.9%) was lower than that of influenza vaccination (63.4%) (Figure 4). The knowledge level

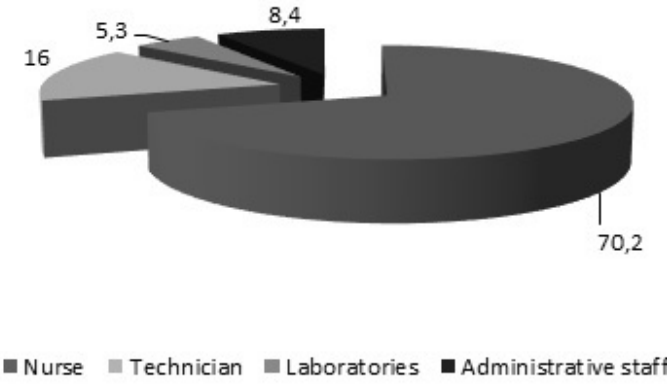

Figure 1. Distribution of the profession, %

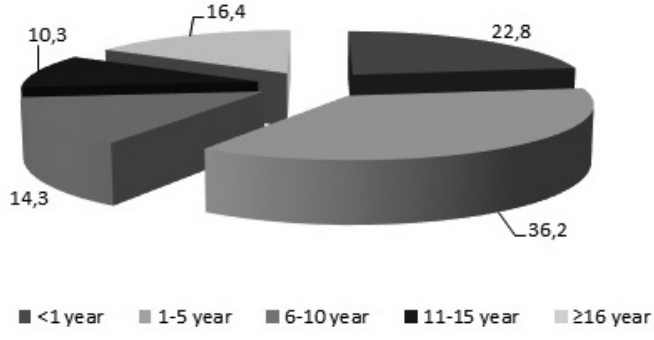

Figure 2. Duration of working in the profession, %

of both influenza and pneumococcal vaccination according to gender are shown in Table I.

Regarding the classification of HCW, the participants who have the working period ≥5 years, the pneumococcal vaccination knowledge level was significantly higher when compared with those with the working period <5 years. (81.6% vs. 54%, p=0.004). Influenza and the pneumococcal vaccines were better known to reduce the risk of infection among the HCW who have a ≥5 years working period when compared with those who have a shorter working period (81.6% vs. 59.7%, p=0.02 for influenza vaccine) (65.8% vs. 35.8%, p=0.003 for the pneumococcal vaccine). According to the working period, the rate of receiving the influenza vaccine was similar (p=0.2).

Only 28.4% of respondents indicated that they had influenza vaccine; the rate of women who had influenza vaccination was higher than that of men, but the difference was not significant (29.4% vs. 24.4%, p=0.51). None of the cases had pneumococcal vaccination. In 75% of influenza-vaccinated participants, the vaccination proposal was made by a physician. Among influenza-vaccinated participants, the proportion of people who thought that vaccination was beneficial was 54.4%. However, 33.8% thought it was not beneficial, and 11.8% had no idea. Not believing that vaccination was efficient (38.7%) and the belief about not being in a risk group (36.1%) were the most common reasons for not vaccinating all participants. In women, the most common reason for not being vaccinated was not believing the efficacy of vaccination, while the belief about not being in risk group was the most common for men (Figure 5).

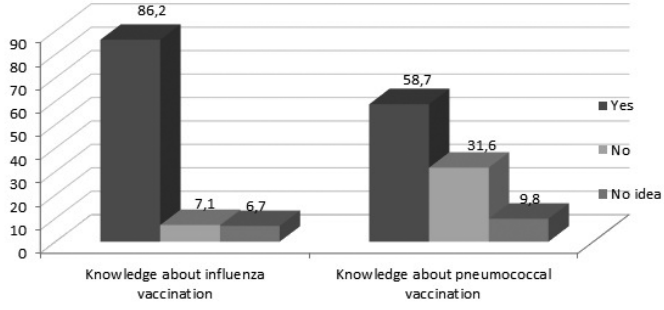

Figure 3. Do you have knowledge about influenza and pneumococcal vaccination? (%)

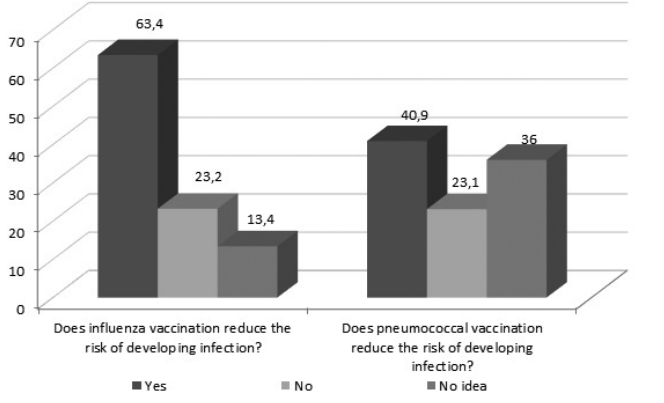

Figure 4. Do vaccines reduce the risk of developing infections? (%)

DISCUSSION

This study demonstrated that the influenza vaccine was better known than the pneumococcal vaccine (86.2% vs. 58.7%). Although the level of knowledge about vaccination was relatively high, the vaccination rates were extremely low among hospital staff. The most common reasons for not vaccinating were the belief that vaccination was inefficient (38.7%) and the belief about not being in a risk group (36.1%).

HCWs have the risk of both acquiring and transmitting influenza. Moreover, every flu season, health care service is disrupted due to the absenteeism of medical staff (7). Therefore, they are an essential target group for influenza vaccination to protect themselves and to prevent transmission to patients (8-10). Annual influenza vaccination for HCW is recommended in most countries (11, 12). However, the vaccination coverage of HCW remains suboptimal worldwide (13, 14).

Influenza can lead to severe illness and serious complications, such as secondary bacterial pneumonia (15, 16). *Streptococcus pneumoniae* is the most commonly isolated microorganism from adults with pneumonia and sepsis (17). Besides, influenza vaccination plays an indirect role in preventing invasive pneumococcal infection, which tends to occur usually during the flu season (3).

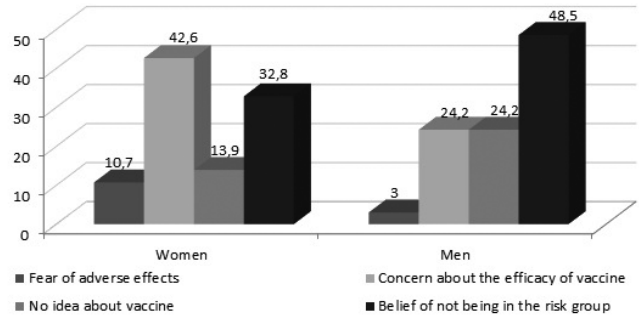

Figure 5. Reasons for not being vaccinated by gender, %

TABLE I. Level of knowledge about influenza and pneumococcal vaccination according to gender

	Women			Men		
	Yes	No	No idea	Yes	No	No idea
Do you have information about influenza vaccination? n(%)	157 (87.7%)	10 (5.6%)	12 (6.7%)	36 (80%)	6 (13.3%)	3 (6.7%)
Does influenza vaccine reduce the risk of infection? n(%)	121 (67.6%)	38 (21.2%)	20 (11.2%)	21 (46. 7%)	14 (31.1%)	10 (22.2%)
Do you have information about pneumococcal vaccination? n(%)	107 (59.4%)	57 (31.7%)	16 (8.9%)	25 (55.6%)	14 (31.1%)	6 (13.3%)
Does pneumococcal vaccine reduce the risk of infection? n(%)	75 (41.7%)	42 (23.3%)	63 (35%)	17 (37.8%)	10 (22.2%)	18 (40%)

In recent years, several studies have been performed to focus on the factors that lead to insufficient adherence to vaccination in Western countries (18, 19). Knowledge gaps, fear of side effects, concerns about the efficacy, and the perception of not being in the risk group seem to be the most common reasons to decline vaccination (20).

Studies show that HCWs knowledge of the influenza vaccine is directly correlated with vaccination uptake (21). It is also reported that getting vaccinated is associated with recommending vaccination to patients. The ratio is 86% versus 54% in vaccinated and unvaccinated HCWs respectively (8).

According to CDC survey, 20% of persons aged ≥65 years reported they received influenza vaccine, but they said that they never had received the pneumococcal vaccine. Some European countries have reported coverage rates of approximately 50% for pneumococcal vaccine among the high-risk population. Most countries do not even report these rates. It is shown by some studies that the most important barrier to vaccinating was that most of the high-risk patients were not even aware that the vaccine existed. This study also showed that health care professionals' advice is the most important factor to be vaccinated (2). Health care providers have a critical role in informing patients about vaccination (6). Many studies showed that vaccine provision by an HCW is found to be an independent predictor of the pneumococcal and influenza vaccine uptake in the elderly (22).

In a meta-analysis sponsored by the CDC, HCWs misconceptions about influenza vaccination were similar to those of the general public (23). Another study by Gresser-Edelsburg et al. (24) reported no difference between HCWs and the general public regarding vaccination support.

These data show that the education of HCWs means the education of the public indirectly. The vaccine coverage among HCWs in the United States is >75% but is <30% in many European countries (25). The mean vaccination coverage rate from 2006 to 2013 flu seasons was 21.6 % ranging from 11% to 34% in Italy (26). Some other recent reports show that the influenza vaccination rate among HCWs differs by seasons and country ranging between 50.8% (Greece 2006–2007) and 35% (Germany 2010–2011) (27).

Our study is in the same line with European studies. Although 63.4% of participants agreed that the influenza vaccine is effective, only 28.4% of them received the vaccine. None of the participants received the pneumococcal vaccine due to the perception of not being in the risk group. Similarly to our study, Çiftci et al. (28) reported the influenza coverage rate of 26.7% among HCWs from Turkey.

In an extensive survey from medical centers in the United States, the most frequent barriers to vaccination were the fear of side effects 39% and fear of contracting influenza from the vaccine 25% (29). Among the whole HCW sample in another study from Turkey, the reasons for declining vaccination included the fear of its adverse effects (31%) and doubts about its efficacy (28.9%) (27). Another barrier to vaccination was a low perceived risk of influenza infection. Haridi et al. (30) reported that 38.9 % of HCWs decline vaccination due to concerns about efficacy.

Similarly, in our study, 38.7% of the participants mentioned not to believe in the efficacy of the influenza vaccine, while 36.1% of them declined due to the perception of not being in the risk group.

Studies indicate that HCWs do not follow recommended immunization practices for adults and themselves. False assumptions and knowledge gaps are the reasons of failing to receive vaccinations. Although the patient and HCWs education is critical in filling knowledge gaps, it has been shown in many studies that knowledge itself is not sufficient to improve immunization practice (27).

Influenza outbreaks in hospitals are related to low vaccination rates among HCWs (28). These outbreaks put patients at an important risk of acquiring the infection, particularly in critical care units. Health care systems have an ethical and moral duty to protect vulnerable patients from influenza (30).

Due to the failure of voluntary immunization programs, mandatory policies are being increasingly adapted to health care centers. A recent review indicated that a mandatory vaccination strategy is the most successful way to increase vaccination uptake. Many health care centers in the United States have implemented mandatory policies with a nearly 100% compliance (30).

To the best of knowledge, this is the first study evaluating the knowledge level of hospital staff about influenza and pneumococcal vaccination in Cyprus. However, there are some limitations to the study. The relatively small study population and the use of a non-validated questionnaire were the main limitations. The results of this study may not reflect the knowledge of all hospital staff in the country since it was conducted in only two hospitals in Cyprus. Furthermore, the definition of the knowledge on vaccination depended on only one question.

We found that the influenza vaccine was better known than the pneumococcal vaccine. Although the level of knowledge about vaccination was relatively high, the vaccination rates were meager among hospital staff in Cyprus. These findings should be used to improve any future vaccination campaigns. Raising the awareness accompanied with mandatory policies seem to be likely effective.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Kyrenia (18/10/2018; ref no: RY-2018-11).

Informed Consent: Written informed consent was obtained from participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.E.; Design – E.Ü.E.; Supervision – F.Y.; Resources – Z.Ö.Y.; Data Collection and/or Processing – S.A.B.; Analysis and/or Interpretation – H.E.; Literature Search – E.Ü.E.; Writing Manuscript – H.E.; Critical Review – F.Y.

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

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Original Article

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Isolation, Identification, and Antibiotic Susceptibility Patterns of *Pseudomonas aeruginosa* Strains from Various Clinical Samples in a University Hospital in Northern Cyprus

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BACKGROUND/AIMS
Pseudomonas aeruginosa is a severe opportunistic bacterium responsible for frequently lethal nosocomial infections. It is highly resistant to commonly used antibiotics, creating a real challenge in the treatment of nosocomial infections.

MATERIALS and METHODS
A total of 152 samples were collected from various departments of the hospital, which included wound, blood, urine, cerebrospinal fluid (CSF), sputum, aspiration fluid, and ear, nose, and throat swab samples. The susceptibility pattern of bacteria was determined by using the BD Phoenix 100 automated microbiology system. *P. aeruginosa* was also identified according to its cultural, microscopic, morphological, and biochemical characteristics.

RESULTS
Samples were identified by using BD Phoenix 100 and conventional biochemical tests are used for confirmation. The results of antimicrobial susceptibility testing indicated that *P. aeruginosa* was sensitive to piperacillin–tazobactam (92.5%), meropenem (87.2%), colistin (86.7%), ticarcillin–clavulanate (86.6%), amikacin (81.5%), imipenem (80.8%), norfloxacin (79.5%), cefepime (78.4%), ceftazidime (76.0%), gentamicin (76.0%), levofloxacin (73.5%), and ciprofloxacin (73.2%). On the other hand, the resistance rates of amoxicillin, ampicillin–sulbactam, cefuroxime, nitrofurantoin, cefoxitin, trimethoprim/sulfamethoxazole, and ceftriaxone were found to be 100%, 98.7%, 97.7%, 97.7%, 94.7%, 94.7%, and 93.8% respectively. The prevalence of antibiotic susceptibility of *P. aeruginosa* in Cyprus is more in males (62.5%) than in females (37.5%).

CONCLUSION
Knowledge about local antimicrobial resistance patterns of *P. aeruginosa* is essential for the guidance of empirical therapy by physicians, medical microbiologists, and public health officials. Antimicrobial surveillance should be done periodically to detect current resistance in our local area.

Keywords: Antibiotic susceptibility, Northern Cyprus, pseudomonas aeruginosa, resistance

INTRODUCTION

Pseudomonas aeruginosa is a gram-negative, bacillus, and non-spore forming bacterium. It is widely distributed in nature including soil, water, and various types of vegetation throughout the world (1, 2). It causes community-acquired and nosocomial infections such as pneumonia, urinary tract infections, and bacteremia. The infections can be particularly important in patients who are immunocompromized, such as neutropenic or cancer patients (3, 4). Nowadays, the rates of morbidity and mortality have been increased because of multidrug-resistant *P. aeruginosa* strains (5).

P. aeruginosa has an intrinsic and acquired resistance against many antibiotics. In addition, it can also gain resistance due to abusive or misuse of commonly used antibiotics (6). The microorganism possesses a natural resistance to antibiotics

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including aminoglycosides, cephalosporins, fluoroquinolones, and penicillins (7). This organism is the most common etiological agent of pneumonia, urinary tract infections, and in the bloodstream (8).

These bacteria have combination resistance mechanisms according to their cephalosporins production, having efflux pumps, low intrinsic outer membrane permeability, and target mutations. Because of this situation, in combination with the misuse of drugs, hospital infections of multidrug-resistant *P. aeruginosa* cause serious problems (9). Clinical isolates of gram-negative rods including *P. aeruginosa* have been shown to produce an enzyme called inducible beta-lactamases, which is the mechanism of bacterial resistance to beta-lactam antibiotics. These enzymes are plasmid-mediated (4). *P. aeruginosa* is isolated from various body fluids including sputum, urine, wounds, eye, ear, and blood. A narrow class of antibiotics is effective against *P. aeruginosa,* including the carboxypenicillins, quinolones, cephalosporins, and aminoglycosides (9, 10). As the antibiotic resistance profiles of *P. aeruginosa* can change in years, prevalence studies must be carried out regularly. The aim of this study was to determine the antibiotic susceptibility of *P. aeruginosa* from clinical samples and to contribute the application of appropriate empiric therapy in the Near East University in Northern Cyprus.

MATERIALS and METHODS

Collection of Samples

This study was carried out at our microbiology laboratory between June 2014 and October 2015. A total of 152 samples were collected from the different units of the hospital. These samples included urine, blood, nasal swab, sputum, aspiration fluids, intravascular catheters, CSF, and wound. All the samples were first processed to get a pure culture by subculturing using general and selective media as blood and eosin methylene blue agar. The demographic information was obtained from the hospital systems. The sensitivity pattern of the bacteria was determined by using an automated microbiology system (Becton-Dickinson, USA) according to the standards of Clinical & Laboratory Standards Institute. Ethics committee approval was not taken due to in vitro design of the study. This study does not include human participants. Thus, no consent form was required.

Statistical Analysis

Statistical Package for the Social Sciences version 22.0 (SPSS IBM Corp.; Armonk, NY, USA) was used for the analysis of the data.

RESULTS

A total of 152 records were identified as *P. aeruginosa* from different specimens and were mostly isolated from urine samples in this study (Figure 1). In our study, 62.5% of the subjects were males and 37.5% were females. Their ages ranged from 10 to 67 years and are presented in Figure 2. When the age distribution was considered, *P. aeruginosa* infections were more frequently seen in the ages between 10 and 20 and over 60. The antimicrobial susceptibility test revealed that *P. aeruginosa* was highly sensitive to most of the antibiotics tested. Piperacillin–tazobactam was the most effective drug against all *P. aeruginosa* (92.5% sensitivity) followed by meropenem (87.2%), colistin (86.7%), ticarcillin/clavulanate (86.6%), amikacin (81.5%), and imipenem (80.8%). On the other hand, *P. aeruginosa* had 98.7% resistance to ampicillin/sulbactam antibiotic and the other high resistance rates were for cefoxitin (94.7%), trimethoprim/sulfamethoxazole (94.7%), and ceftriaxone (93.8%) (Table 1).

DISCUSSION

According to the scientific studies, multidrug-resistant strains for both the hospitals and community constitute a serious problem, especially infections, induced by *P. aeruginosa* across the world (4). *P. aeruginosa* is a nosocomial bacterium, which is present in disinfectants, respiratory equipment, sinks, taps, and mops in the hospital by forming a biofilm (1). A total of 152 records were identified as *P. aeruginosa* from different specimens and were mostly isolated from urine samples in this study (Figure 1). Regarding gender, 62.5% of the subjects were males whereas 37.5% were females. It is reported that infections caused by *P. aeruginosa* are more common in males than females. This is comparable with other studies that detected 61% of pseudomonas infections in males (11).

The ages of the patients ranged from 10 to 67 years (Figure 2). When the age distribution was considered, *P. aeruginosa* infections were more frequently seen in the ages between 10–20 and over 60 years. Our results are likely similar to other studies that

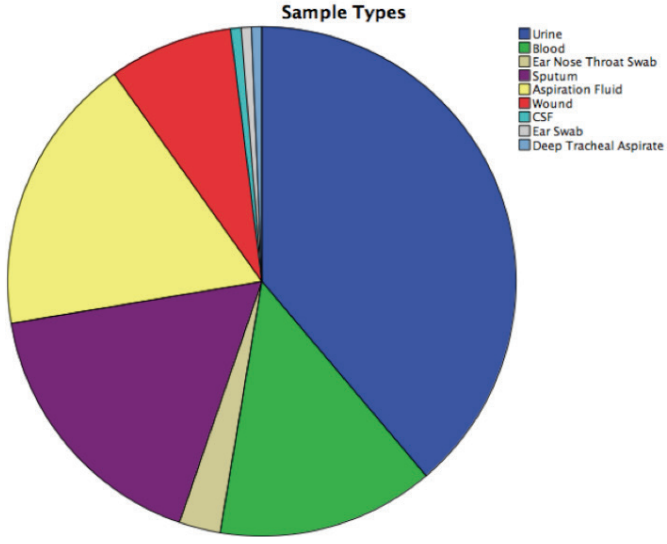

Figure 1. Distribution of *P. aeruginosa* among different samples

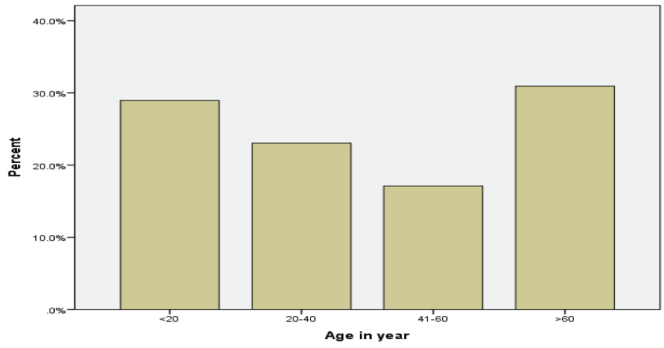

Figure 2. *P. aeruginosa* isolates from different age groups

TABLE I. Antimicrobial susceptibility pattern of *Pseudomonas aeruginosa*

Drugs	Total	Sensitive Count (%)	Intermediate Count (%)	Resistant Count (%)
Amikacin	151	123 (81.5)	8 (5.3)	20 (13.2)
Ampicillin/Sulbactam	151	2 (1.3)	-	149 (98.7)
Aztreonam	152	76 (50.0)	18 (11.8)	58 (38.2)
Cefepime	148	116 (78.4)	19 (12.8)	13 (8.8)
Cefoxitin	151	8 (5.3)	-	143 (94.7)
Ceftazidime	150	114 (76.0)	5 (3.3)	31 (20.7)
Ceftriaxone	113	7 (6.2)	-	106 (93.8)
Ciprofloxacin	149	109 (73.2)	5 (3.4)	35 (23.5)
Colistin	113	98 (86.7)	-	15 (13.3)
Gentamicin	146	111 (76.0)	8 (5.5)	27 (18.5)
Levofloxacin	113	83 (73.5)	4 (3.5)	26 (23.0)
Imipenem	151	122 (80.8)	7 (4.6)	22 (14.6)
Meropenem	149	130 (87.2)	6 (4.0)	13 (8.7)
Piperacillin/Tazobactam	148	135 (92.5)	-	17 (11.5)
Ticarcillin/ Clavulanate	144	64 (86.6)	-	46 (42.6)
Trimethoprim/ Sulfamethoxazole	150	7 (4.7)	1 (.7)	142 (94.7)

found 43.5% *P. aeruginosa* infection in the age range of 1–15 years. Studies reported that incidence of *P. aeruginosa* increased with age and was higher in males than females (11, 12). Ak et al. (6) reported that the highest resistance was observed for levofloxacin (13%) whereas the lowest resistance was observed for amikacin (3%) in Malatya. Aykan and Çiftçi (13) investigated the antibiotic resistance of *P. aeruginosa* isolates over 11 years (2003–2013) in Turkey. They reported that carbapenem resistance like imipenem resistance increased between 2007 and 2009; otherwise, these changes were not statistically significant for imipenem or meropenem. Resistance to aminoglycoside antibiotics such as amikacin, gentamicin, netilmicin, and tobramycin was decreased, but these changes were not found statistically significant. These study groups concluded that the antibiotic resistance in *P. aeruginosa* has started to decrease in Turkey.

In our study, the antimicrobial susceptibility test revealed that *P. aeruginosa* was highly sensitive to most of the antibiotics tested. Piperacillin/tazobactam was the most effective drug against all *P. aeruginosa* strains (92.5% sensitivity) followed by meropenem (87.2%), colistin (86.7%), ticarcillin/clavulanate (86.6%), amikacin (81.5%), and imipenem (80.8%). On the other hand, *P. aeruginosa* had 98.7% resistance to the antibiotic ampicillin/sulbactam and the other high resistance rates were observed for cefoxitin (94.7%), trimethoprim/sulfamethoxazole (94.7%), and ceftriaxone (93.8%) (Table 1). Ruh et al. (14) studied the antibiotic resistance of *P. aeruginosa* between 2010 and 2014 in Northern Cyprus and reported that the resistance rate for aztreonam was 42.9% and susceptibility rate for levofloxacin was 79.8%. According to our results, the resistance rate for aztreonam (38.2%) and the susceptibility rate for levofloxacin (73.5%) decreased in a one year period (2014–2015) in Northern Cyprus. In the present study, aminoglycoside (gentamicin 18.5%; amikacin 13.2%), fluoroquinolone (ciprofloxacin 23.5%; levofloxacin 23%), and ceftazidime (20.7%) resistance among *P. aeruginosa* isolates were found to be higher with the rates reported in the antimicrobial resistance report of Southern Cyprus between 2012 and 2015 (15).

The present study shows that the clinical isolates of *P. aeruginosa* are resistant to commonly used antibiotics and achieve more resistance to the newest antibiotics. In Cyprus, piperacillin/tazobactam, and meropenem are the most effective agents against *P. aeruginosa* whereas ampicillin/sulbactam, cefoxitin, and trimethoprim/sulfamethoxazole have the highest resistance. The knowledge of local antimicrobial resistance patterns is necessary to guide empirical therapy applied by practicing physicians, medical microbiologists, and public health officials.

Ethics Committee Approval: Ethics committee approval was not taken due to in vitro design of the study.

Informed Consent: N/A.

Author Contributions: Concept: M.G., K.S.; Design: K.S., A.A.; Supervision: K.S.; Resource: K.S., E.G.; Materials: E.G., M.G.; Data Collection and/or Processing: E.G., M.G., A.A.; Analysis and/or Interpretation: A.A., E.G., K.S.; Literature Search: E.G., M.G.; Writing; E.G., M.G.; Critical Reviews: K.S., M.G., A.S., E.G.

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

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

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Epidemiological Surveillance of Rotavirus and Adenovirus among Patients with Acute Gastroenteritis: A Single-Center Experience in Northern Cyprus

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BACKGROUND/AIMS
The aim of this study was to determine the prevalence of rotavirus and adenovirus in patients with acute gastroenteritis referred to a tertiary hospital in Northern Cyprus and to investigate the distribution of viral infections according to age, sex, and season of the year.

MATERIALS and METHODS
In this retrospective study, a total of 503 stool samples for rotavirus and 490 samples for adenovirus detection from 527 patients were received and examined in the hospital microbiology laboratory between September 2015 and September 2018. A qualitative immunochromatographic rapid antigen test was used for viral antigen screening in stool specimens collected from participants.

RESULTS
In 96 out of 527 patients with acute gastroenteritis in the age group 0–92 years, at least one of the rotavirus and/or adenovirus antigens was detected as positive. Sixty-four (12.7%) of 503 screened patients were positive for the rotavirus antigen, while the adenovirus positivity was detected in 47 (9.6%) of 490 patients. Ten (1.9%) patients were positive for both viral antigens. The positivity of adenovirus was significantly higher in males than in females ($p<0.05$; $p=0.038$). Rotavirus-positive (n=30, 46.9%) and adenovirus-positive (n=31, 66%) cases were identified as the most common in the age group 0–2 years. Both viral antigens were observed most frequently in the summer season (rotavirus, adenovirus: $p>0.05$; $p=0.215$, $p=0.518$, respectively).

CONCLUSION
Acute viral gastroenteritis was most prevalent in the age group 0–2 years among the patients. Rotavirus and adenovirus gastroenteritis could be detected during all seasons in Northern Cyprus, highlighting the importance of rotavirus surveillance particularly in the summer months.

Keywords: Adenovirus, Cyprus, epidemiology, gastroenteritis, rotavirus

INTRODUCTION

Acute gastroenteritis (AGE), characterized by the sudden onset of symptoms, including diarrhea, nausea, vomiting, and abdominal pain, is a major cause of morbidity and mortality worldwide, and it can be life-threatening, particularly for young children in underdeveloped and developing countries. AGE is caused by a range of bacterial, viral, and parasitic pathogens, as well as by toxins, chemicals, and other noninfectious agents. While the implementation of increasing hygiene and preventive measures has significantly reduced the number of cases of bacterial and parasitic AGE, an increase in the frequency of viral infections and outbreaks has recently been observed in Europe and the United States (1, 2). Approximately 1.3 million deaths worldwide are attributed to diarrheal diseases (3). While both community-acquired diarrhea (CAD) and hospital-acquired diarrhea (HAD) are associated with increased health care costs, including treatment

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and hospitalization, in developing countries, rotavirus gastroenteritis alone results in 27 million hospital and outpatient visits and 527,000 deaths among children <5 years of age, with an estimated annual treatment cost of $325 million and total societal costs of $423 million (4).

Gastroenteritis is the second leading cause of infectious-disease-related deaths in children <5 years of age, and viruses are recognized as the most common known agents of AGE (5-7). Among these, adenovirus and rotaviruses are frequently identified as etiological agents of gastroenteritis, and they are responsible for the majority of hospital admissions in infants and children (8). In childhood infections, the etiological agents and severity of the disease vary with age, season, and geographical regions. Therefore, an accurate detection of causative agents in AGE cases is critical in treatment and follow-up.

Rotaviruses are double-stranded RNA viruses, which are transmitted via the fecal–oral route, and they commonly lead to epidemic outbreaks that present with fever, vomiting, and diarrhea, particularly during the winter season. Considered as the most common cause of all severe gastroenteritis in newborns and children worldwide, rotaviruses are responsible for 20%–50% of viral gastroenteritis cases (9, 10). Epidemiological studies show that the percentage of rotavirus gastroenteritis is 20%–40% in Europe, 40%–50% in America, 30%–50% in Asia, and 10%–65% in Africa, while this rate varies between 10% and 40% in Turkey (11-14). Rotavirus gastroenteritis is also associated with a significant economic burden for the health care system, including medical visits, hospitalizations, and treatment costs, as well as for families accounting for the parent work days lost and childcare related costs (15).

Enteric adenoviruses represent other important etiological agents of serious gastroenteritis among infants and young children. Of the 57 identified adenovirus types, only adenoviruses type 40 and 41 were been reported to be associated with diarrhea (16). Adenovirus-induced AGE is spread predominantly by the fecal–oral route and is associated with protracted diarrhea that may contribute to infant dehydration and malnutrition (17). Similar to rotavirus, infection with adenovirus can cause severe disease, increased mortality, and a prolonged hospital stay (18).

The detection of viral gastroenteritis agents is highly important in terms of local epidemiology, monitoring, and surveillance of the disease, which would allow timely implementation of control measures. To the best of our knowledge, there are no data available for the epidemiological surveillance of rotavirus- and adenovirus-associated AGE in Cyprus in the literature. Therefore, in this study, we aimed to screen stool specimens of patients from all age groups, admitted to a tertiary hospital in Cyprus and diagnosed with AGE, for rotavirus and adenovirus antigens, and to determine the prevalence and the distribution of these viruses according to sex, age, and season of the year.

MATERIALS and METHODS

Study Setting

The study was performed at Near East University Hospital in Northern Cyprus. This hospital has 500 inpatient beds and serves about 146,000 outpatients and 6,500 inpatients; approximately 3,000 surgeries are performed annually.

Due to the retrospective nature of the study, no ethical approval was required. The study was conducted according to the Helsinki Declaration. All patient data were anonymized, therefore no informed consent was required.

Specimen Collection

Acute diarrhea is defined as three or more loose or looser-than-normal stools within a 24 h period. Fecal specimens from 527 patients (n=195, 37% inpatients; n=332, 63% outpatients) diagnosed with AGE in the hospital and related clinics between September 2015 and September 2018 were included into this retrospective study. Out of the 527 clinical specimens, 503 were screened for rotavirus, whereas 490 of the stool samples were investigated for the presence of adenovirus as requested by the physician. Demographic features of all cases were recorded. Data from patients who were positive for the presence of parasites in stool microscopy and/or positive for the parasite antigen tests and who were found to be positive for *Salmonella* spp./*Shigella* spp. cultures were excluded from the study. Patients who had diarrheal symptoms at admission or developed diarrhea symptoms within 48 h of admission were considered to have CAD. If symptoms occurred ≥48 h after admission, then HAD was assumed.

Laboratory Virus Antigen Testing

Stool samples were screened using the qualitative immunochromatographic rapid test kit (BioNexia BioMérieux, Marcy-l'Étoile, France) for rotavirus and adenovirus antigen screening according to the manufacturer's recommendations.

Statistical Analysis

Medical records for enrolled study participants were reviewed, and information such as sex, age, date of sample collection, and diagnosis at admission was collected. The distribution analysis of rotavirus and adenovirus prevalence according to gender, age, and season was performed with the Statistical Package for the Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA), using Pearson's chi-square and Fisher's exact tests for statistical analysis. A p-value <0.05 was accepted as statistically significant.

RESULTS

Diarrhea Classification

This study enrolled 527 individuals with diarrheal symptoms. A total of 479 of the cases (90.9%) were defined as CAD, and 48 of the cases (9.1%) were defined as HAD.

Rotavirus and Adenovirus Detection Rates

A total of 527 patients with AGE were included in this study. Patient specimens were subjected to rotavirus (n=503) and adenovirus (n=490) antigen screening. Study participants were in the age group 0–92 years, in which 272 (51.6%) of the patients were males, and 255 (48.4%) were females. While 64 of 503 (12.7%) patients were detected to be positive for rotavirus antigen, 47 of 490 (9.6%) patients were positive for adenovirus antigen. Ten patients (1.9%) showed positive results for both antigens, whereas 96 patients (18.2%) were positive for at least one of the two antigens tested.

Rotavirus and Adenovirus Detection Rates According to Sex

Among rotavirus-positive patients, 38 (59.4%) were males, and

26 (40.6%) were females. In adenovirus-positive patients, 31 (66%) were males, and 16 (34%) were females. The adenovirus positivity was significantly higher in males than in females (p<0.05; p=0.038), whereas no statistically significant difference was observed for rotavirus positivity between males and females (p>0.05; p=0.201) (Table I).

Rotavirus and Adenovirus Detection Rates by Age Group

The median age of study participants was 11.2 (range, 0–92 years). Rotavirus-positive (n=30, 46.9%) and adenovirus-positive (n=31, 66%) cases were most commonly observed in the age group 0–2 years. When cases of viral antigens were evaluated according to age groups, the prevalence of adenovirus was observed to be most frequent in the 0–2 years age group and to be particularly high in the 0–5 years age group, which was statistically significant (p<0.05; p=0.000). On the contrary, there was no statistically significant difference between the age groups of patients for rotavirus positivity (p>0.05; p=0.539) (Table I).

Seasonality of Rotavirus and Adenovirus

Among patients with AGE, both viral antigens were most commonly found during the summer. As shown in Figure 1, 22 (34.4%) of the patients were detected as positive for the rotavirus antigen, and 17 (36.2%) of the patients were detected as positive for the adenovirus antigen in the summer months. Both of the viruses were most frequently observed in June, while rotavirus was equally observed in February. There was no statistically significant difference between the positivity for both antigens with respect to seasonal distribution (rotavirus, adenovirus: p>0.05; p=0.215, p=0.518, respectively). The distribution of viral antigens according to months is shown in Figure 2.

TABLE I. Distribution of the rotavirus and adenovirus positivity according to the age group and sex

Age groups	Rotavirus positivity n (%)	Adenovirus positivity n (%)	Total positive patients n (%)
0–2	30 (46.9)	31 (66)	61 (55)
3–5	12 (18.8)	13 (27.7)	25 (22.5)
6–14	10 (15.5)	2 (4.2)	12 (10.8)
>14	12 (18.8)	1 (2.1)	13 (11.7)
TOTAL	64 (100)	47 (100)	111 (100)
p	0.539	0.000*	
Sex			
Male	38 (59.4)	31 (66)	69 (62.2)
Female	26 (40.6)	16 (34)	42 (37.8)
TOTAL	64 (100)	47 (100)	111 (100)
p	0.201	0.038*	

*p<0.05 significant

DISCUSSION

Diarrheal diseases represent a major health problem, particularly for children in developing countries. Data from a plethora of studies indicate that more than 1 billion children are referred to hospitals due to diarrheal symptoms each year, and approximately 700,000 children lose their lives because of diarrheal diseases (19). Viral gastroenteritis is the leading cause of diarrheal disease representing 30%–40% of all cases reported. Detection of the causative agent of AGE that is viral in origin is critical for an appropriate treatment and implementation of preventive measures. Epidemiological factors such as age, season of the year, and geographic features, in addition to laboratory tests and clinical characteristics, have been proven as useful in differential diagnosis. To the best of our knowledge, this study represents the first epidemiological surveillance report of viral gastroenteritis in Cyprus. In this 3-year retrospective study, the prevalence of acute viral gastroenteritis was found to be 18.2%, providing evidence supporting its importance in childhood diarrhea.

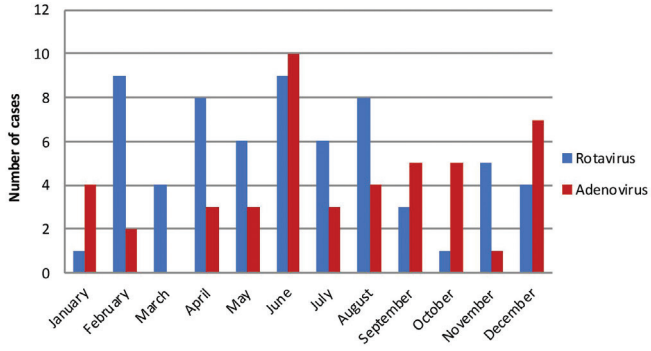

Figure 2. Monthly distribution of rotavirus and adenovirus gastroenteritis

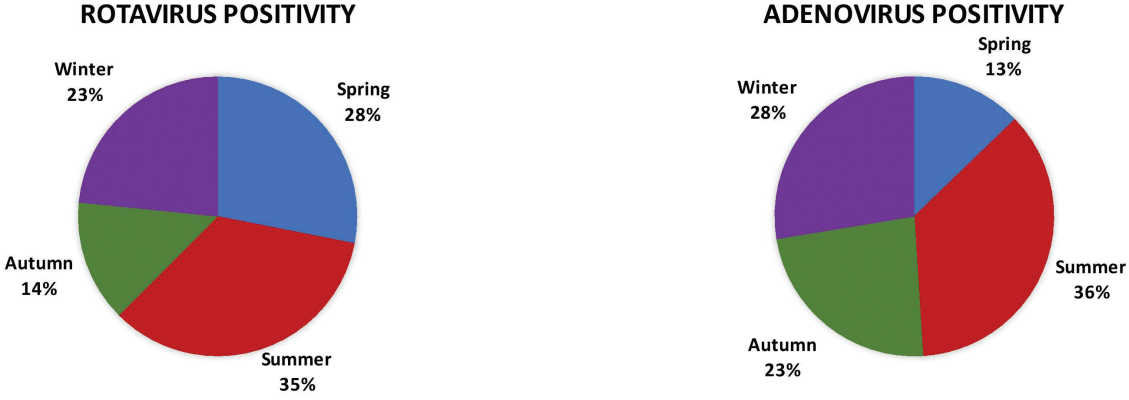

Figure 1. Seasonal distribution of rotavirus and adenovirus positivity

While also commonly seen in adults, rotaviruses and enteric adenoviruses are among the most important agents of viral gastroenteritis in children. Rotavirus-induced gastroenteritis usually presents for 5–8 days with fever and vomiting. The clinical scenario in neonates and children, if not treated, may be fatal due to electrolyte and fluid loss. Although the incidence of rotavirus infections varies according to age and season, they are responsible for 20%–50% of AGE cases worldwide (10, 11). Positivity rates of rotavirus and adenovirus may also vary in different geographical areas due to different detection methods and targeted populations. The prevalence of rotavirus in AGE patients in Turkey during the 2013–2015 period was 14.8% (20). In France and Spain, epidemiological data indicate that the prevalence of rotavirus-associated AGE is 21%. The same incidence is 35% in Italy and 38% in Finland, while in China, the rotavirus positivity among CAD and HAD cases was reported as 22% (21-24). In our study, the incidence of rotavirus gastroenteritis was 12.1% in all CAD and HAD cases investigated in Cyprus, consistent with studies conducted across Turkey.

Adenoviruses are the second leading cause of acute and prolonged diarrhea after rotaviruses. Among them, enteric serotypes 40 and 41 from the subgenus F are most frequently associated with gastroenteritis. Studies from multiple countries indicate that the frequency of adenovirus-induced viral gastroenteritis ranges between 6% and 30%. In England, data collected from 116 UK children confirmed the presence of adenovirus in 12% of cases investigated, while a 5-year study from Ireland indicated the prevalence of gastroenteritis with adenovirus origin at 13.7% (25). In Italy, the rate of detection of enteric adenoviral gastroenteritis in pediatric population was 23% (26). In a pediatric ward in Iran, the adenovirus positivity in children aged <5 years was reported to be 14% and 8%, for adenovirus serotypes 40 and 41, respectively (27). Similarly, in one of the first reports on enteric adenoviruses in India, data from three different cities and 439 hospitalized patients revealed the virus incidence as 7%–9% (28). In a study by Qui and colleagues (29), the adenovirus positivity was detected in 79 (28.9%) of 273 children with diarrhea, including seven different serotypes (human adenovirus 40, 41, 3, 2, 1, 5, and 57) in China. On the other hand, a marked decrease in rotavirus detection was observed among unvaccinated preschool children in the Netherlands during the rotavirus season (January–April), where the rates of positivity were as low as 0.6% in 2014 compared to 11.2%, 6.9%, 6.8%, and 6.7% in 2010, 2011, 2012, and 2013, respectively (30). When pediatric age groups are evaluated, epidemiological data from Turkey demonstrated that the highest viral antigen positivity in children 13–24 months of age was 24.5% and 8.2% for rotavirus and adenovirus, respectively (20). In the study conducted by Hamkar et al. (31), it was shown that the rotavirus positivity was most frequently seen in the group aged <1 year, while the adenovirus positivity was detected predominantly in the age group 2–5 years. In our study, the prevalence of adenovirus in children aged 0–5 years was 12% (n=44/352), 1.9% (n=3/138) in cases older than 5 years, and 9.6% (n=47/490) in all age groups. Consistent with previous reports, our data suggest that adenoviruses are more frequently seen in children aged 0–5 years.

When previous studies on the association of demographic data and incidence of rotavirus and adenovirus gastroenteritis were analyzed, no statistically significant relationship was found between the two viral antigens and gender (32-34). In our study, there was no statistically significant relationship between rotavirus gastroenteritis and gender, whereas adenovirus gastroenteritis was significantly higher in males. Similarly, a number of previous studies reported that adenovirus gastroenteritis is more common in males (34, 35), although a few reports indicated no statistically significant association between adenovirus gastroenteritis and gender (36, 37).

The seasonal distribution of rotaviruses is well known. Global surveillance studies show that rotaviruses are the leading cause of gastroenteritis, typically starting in autumn and continuing during the winter months with a peak of viral gastroenteritis hospitalizations in the winter. In their landmark study, Cook et al. (38) demonstrated that rotaviruses had a distinct seasonal peak in countries with temperate climates but were seen year-round in the tropical setting. A large cohort study in hospitalized pediatric patients in Germany indicated that rotavirus infections are most frequently observed from January to April, while adenoviruses were detected mainly in December with a second peak in March (39). Although adenovirus infection rates are similar in every period of the year, there is a trend of statistically insignificant increase in summer months. In the study by Bicer et al. (40), it was emphasized that summer was the peak season for enteric adenovirus infections, with July (17.3%) and August (20.9%), having the highest incidence rates. Our results indicate that both viral gastroenteritis agents were most commonly detected in the summer, although this was not statistically significant. Due to the Cyprus climate, which is hot in the summer and mild with low rainfall rates in the winter, the viral pathogens can be found at similar rates during different seasons. Data obtained in this study highlight that the surveillance of rotavirus gastroenteritis in summer months is of critical importance. The number of patients included in this study and the lack of screening for both viral antigens in each patient sample were among the limitations of this study.

To the best of our knowledge, this study represents the first report of epidemiological characteristics of rotavirus- and adenovirus-associated AGE in Cyprus. AGE associated with the viral pathogens studied was most commonly observed in the age group 0–2 years, whereas both agents were responsible for enteric infections in other age groups. Our findings highlight that rotavirus and adenovirus infections can be seen among patients with AGE during all seasons on the island, with adenovirus infections being more frequently observed in males. In summary, we conclude that the early diagnosis of viral pathogens in patients with AGE and the implementation of a multicenter surveillance system in Cyprus will prevent severe disease manifestations and would allow rapid and more effective prevention strategies.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Due to the retrospective nature of the study, informed consent was not required. Patient data were anonymized.

Peer-review: Externally peer-reviewed.

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How To Achieve Effective Teamwork: The View of Mental Health Professionals

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BACKGROUND/AIMS
The nature of multidisciplinary teamwork in mental health care is diverse and complex. However, effective teamwork is still one of the main means to achieve the expected outcomes in the mental health field. Since teamwork requires face-to-face relationships, it is important to sharing meanings to provide effective care. This study aimed to explore how mental health professionals describe teamwork and to reveal difficulties they face and provide solutions from their own professional standpoint.

MATERIALS and METHODS
This exploratory qualitative study was conducted at psychiatry departments of three university hospitals. The critical case technique was used as a purposive sampling method. Semi-structured interviews were conducted with 15 health professionals, including psychiatrists, nurses, social workers, and psychologists who worked at psychiatric inpatient units. Thematic analysis was applied in data evaluation.

RESULTS
The themes were categorized under three headings: concepts, barriers, and suggestions. Sharing the tasks and mutual acceptance of roles were the factors most stated as necessary for achieving effective teamwork in the inpatient unit. Avoidance to take responsibility, strict hierarchy, underestimating the roles of other team members, personalization of problems, an inadequate number and qualification of staff, and a rapid staff turnover were remarkable obstacles. Participants stressed the importance of a work environment that focuses on the needs of patients and open communication.

CONCLUSION
In this study, we tried to explain the subjective dimension of the possible reasons of the failure to achieve teamwork in mental health care provision. The findings suggest that mental health professionals used similar concepts when explaining teamwork. However, they had different ideas about how to shape and conduct teamwork.

Keywords: Mental health care, mental health professionals, qualitative research, teamwork

INTRODUCTION

In health care provision, needs of patients are diverse and change over time, while the roles of health care professionals are often flexible, and leadership changes depending on the required expertise. That is why achieving effective multidisciplinary teamwork is a sine qua non in providing high-quality services, research, and education in health care (1-4). Many authors have addressed the benefits of effective teamwork, such as a reduced hospitalization rate and costs, an improved service provision, enhanced patient satisfaction, and staff motivation and innovation. However, studies show that it is difficult to achieve effective teamwork. Thus, a significant percentage of medical errors has been attributed to communication breakdowns caused by lack of effective teamwork (3-8).

Multidisciplinary work, facing obstacles in every field of health care, is more difficult in mental health care services due to a high degree of uncertainty and interdependence. Since the role is more certain among the professionals in other medical areas, teamwork usually does not create as much of a threat as it does in mental health teams. However, role boundaries still represent an ambiguous issue for mental health care and need to be addressed so that we can reach optimal outcomes (3, 5-7, 9).

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Although each mental health professional introduces himself or herself as nurses, doctors, or psychologists, they are all working with individuals, families, and groups for similar goals, such as increasing the self-confidence of the patient, improving problem-solving and life skills, including social interactions. The overlap of roles in these conditions is natural, and it is difficult to determine the role boundaries. That is why achieving effective teamwork is very challenging. In such cases, roles should be integrated for the patients' benefit rather than struggling to separate them (1, 6, 7, 10, 11).

A constant discipline-specific language in a multidisciplinary environment can create a silo effect in the health care services (12). For this reason, to achieve an effective teamwork, shared mental models, and open communication are crucial. That is, common understanding about teamwork can facilitate and increase communication in clinical settings, especially in mental health area (13). Teamwork needs a set of interrelated behaviors and actions that occur among workers while performing a task. That is why team members should share discuss information about the patient by keeping in mind that the roles under the surface are transitive. However, there are differences in perceived roles in the team, and these differences are due to different training and professional socialization of the members (14, 15).

Difficulties in establishing and maintaining effective teamwork usually have been attributed to the lack of communication, lack of collaboration and shared decision making, and differences in professional education (7, 8, 16-18). If we think of health care as of a large puzzle, each intradisciplinary team is like one special piece of this puzzle. The uncertainity about the team and teamwork definitions determines the nature of communication, creating ambiguity and role conflicts and causes non-conformity in the parts of the puzzle. Differences in definitions of the teamwork change the way of the communication, regardless of how skillful the person is or how qualified and/or expert (8, 16, 17). Thus, shared meanings, as noted in Lo (19), can help professionals to visualize the whole puzzle.

In this study, we aim to show the perception of mental health professionals using their own language. The purpose of the study is to describe effective teamwork from the perspective of mental health professionals and to explore concepts from their own point of view. We examined which concepts the mental health care team members use to describe teamwork, and how they define problematic teamwork areas.

MATERIALS and METHODS

Participants and Setting

This exploratory study was conducted at inpatient psychiatry units of three university hospitals in Ankara, Turkey. The critical case technique as a purposive sampling method was used in the study. This sampling method is a widely used method in qualitative research, where the sample consists of individuals being selected because they are especially knowledgeable about or experienced with a phenomenon of interest. A referral sampling was used to reach the participants. These health professionals were psychiatrists, nurses, social workers, and psychologists. The inclusion criteria were 1 year of experience working in an inpatient psychiatric unit.

The working style was very similar among these three hospitals. Each inpatient unit had a 35–45-bed capacity. Each discipline had specific responsibilities. For instance, psychiatrists were the team members who decided to admit and discharge patients. Psychologists were usually administering the tests to help the diagnosis, and the nurses were responsible for all functions of inpatient care. Social workers were doing family interviews. However, the roles of each discipline were complementary related to the treatment and recovery process.

Participation in the study was voluntary, and all participants gave verbal consent. The first two authors of this study interviewed the respondents. After being given information about the study and accepting to participate, the interviews were initiated and tape-recorded.

Twenty-four health professionals were invited to participate in the study, and 15 volunteered to participate (6 nurses, 2 social workers, 3 psychologists, and 4 psychiatrists). Of participants, 10 were women and 5 were men. The number of professional experience years ranged from 1 to 30 years. The professionals who did not want to participate in the study usually said they had no time for the interview. However, all of them helped the researchers to approach another person who would have time for the interview. The participants mostly started to talk broadly, including localized daily problems in the work environment, and interviews were conducted until the theme saturation was achieved.

Data Collection

Interviews were conducted in the participant's workplace in a private room individually in Turkish. Participants did not meet the researchers personally before the study. Two two authors of this study who were pschiatric nursing faculty, interviewed the respondents. They were experienced in interviewing techniques.

There was an interview guide consisting of three open-ended questions for interviews. In order not to direct the participants' answers to a particular issue, the questions were quite general. The questions were

- Could you explain your definition of a team or the idea of teamwork?
- How would you describe effective teamwork?
- What should be done to improve teamwork?

In addition, interviewers also asked if they had any formal/specific education or training about teamwork. During the interview, probes were used when needed. The interviews ranged from 30 to 60 minutes. All interviews were audio recorded and transcribed verbatim.

Data Evaluation

Authors used thematic analysis for data evaluation. Thematic analysis had the following six steps: familiarization with the data, generating initial codes, searching for themes, reviewing themes, defining/naming themes, and producing the report. "Coding" refers to the creation of categories in relation to data; the grouping together with the different instances of the datum under an umbrella term that can enable them to be regarded

as "of the same type" (18). The constant comparison approach was applied, and emerging themes were refined and compared with the data. In the formulation process of the themes, authors re-evaluated the statements independently to strengthen the validity of the themes.

Since the study did not involve any interventions or include a vulnerable population, and since it was based on the thoughts of professionals, a formal ethical approval was not required for this study. In accordance with the Declaration of Helsinki, written and verbal information about the study and the nature of the study was provided to the participants, and their verbal consent was obtained before the interviews. The participants were informed verbally about the purpose, privacy, and voluntary basis of the research and that they were free to terminate the interviews whenever they wanted. Participants who gave informed consent were interviewed.

RESULTS

Under the three main categories, 6 subthemes emerged (Table I). The categories were the following: "concepts embodied in teamwork definition," "barriers to teamwork," and "suggestions for effective teamwork." Categories and theme-related quotes of the participants were given in the following. Each number after the statement refers to one participant.

None of the participants had any formal/specific education or training about teamwork. Their statements were usually based on their own work experiences. They stated that they could talk about their personal inferences only that is, about how they formed their teamwork view and definitions in their course of working years.

Category I. The Concepts Embodied in Teamwork Definition

Participants, defining teamwork, mostly focused on leadership. They also emphasized sharing tasks by addressing patient needs as central part. In addition, admitting the roles of other team members during the teamwork are important components, as well as open communication.

Team members emphasized the importance of good quality leadership. A team leader was mentioned as the person responsible for maintaining a motivating environment. Participants noted that acknowledging roles of other team members was as crucial as professional competence. However, they stated that roles sometimes might change according to the specific needs of patients and professional competencies of the team members. In addition, to be able to achieve teamwork, focusing on patients' needs was an important component. Examples of statements were as follows:

...The personality traits of the manager are very important. However, being a leader takes time, and it is very important to be a role model (R9).

...The team leader should understand that every person has different motivation resources and should take some preventive

TABLE I. Categories and subthemes

Categories	Themes
Category I: The concepts embodied in teamwork definition	The concepts
	Good quality leadership
	Focusing on patient needs
	Professional competence
	Open communication
	Acknowledging other team members' roles and contribution
Category 2: Barriers to teamwork	Individual-related barriers
	Avoiding responsibility/pass the buck
	Devaluing and trivializing others' contributions and roles
	Personalization of the problems
	Not to collaborate
	Organization-related barriers
	Strict hierarchy
	Staffing problems; rapid changes in staff, lack of staff
Category 3: Suggestions for effective teamwork	Competent leadership
	Supporting the leaders to improve their leadership traits
	Creating an effective communication atmosphere
	Structured team meetings to give everyone the right to speak
	Establishing an information flow to improve collaboration
	Supporting team members financially and for personal development
	Improving personal characteristics (respectfulness; being tolerant and unprejudiced, flexibility; ability to listen, openness toward criticism)
	Reducing financial problems

measures to motivate each person. They also create a dynamism and cohesion in the team (RI2).

... Of course, every professional should know his or her own job very well. However, they also should know about the other team members' jobs or try to know about them and must appreciate what others do... (RI0).

...Teamwork means sharing the tasks... Whatever the focus of us, everyone in the team should do their best; they should do whatever they know best. I mean the tasks should be shared... (R6).

...For me, it is an integration of every task, and work has been done focusing on patient's needs... (R2).

... This is a 24/7 continuous service. For this reason, every person in the team should focus on the patients and their needs. Focus must be on the patient... (RI).

The other valued concept was communication. Communication was considered crucial to provide effective teamwork.

...While doing your job, you should be aware of working in a team and communicate with each member openly. Otherwise, you cannot provide collaboration... (R3).

... For teamwork, being unprejudiced is important. You can have opposite thoughts or opinions, but respect is crucial (R8).

In summary, leadership was a fundamental factor affecting communication and role performance. Role clarity and professional qualifications are important, but patient needs should be prioritized.

Category 2. Barriers to Teamwork

Under this category, two main themes emerged as "individual-related barriers" and "organization-related barriers." Individual-related barriers included negative attitudes including avoiding responsibilities, devaluing and/or trivializing contributions and roles of other team members, personalization of problems and working alone, and/or not being able to collaborate. According to participants, if a team member is not a good collaborator and is working alone, or not taking responsibility when needed, it is obvious that conflicts among team members and needs of patients will be unmet.

...If the person says that "This is not my task," "I do not want to do that," or "I'm tired, someone else must do it" etc., it blocks the communication channels and prevents teamwork. People who ask, "Is this our job?" and who are not motivated to work interfere with the motivation of team (RI0).

... To progress in the treatment plan, all the professions should contribute to the work. It is for the benefit of the patients. If there is collaboration in the team, you can see the outcomes fast... (RI0).

...Some of my colleagues say to me, "these are physicians' tasks; we should not do that. If we do it, it becomes as our task in time"... these statements make me confused. There is a task, but nobody takes the responsibility, but in fact, this is for patient, it is not for someone else (RI).

... Here, everybody is aware of his or her own limits. Sometimes inexperienced new people may break the role limits. If you see any conflict in the team, this is mostly the main reason (RII).

... We need not to personalize everything around us. Focus must be on the patient... (RI).

Participants addressed that each team member must believe in the effectiveness of teamwork. "Avoiding sharing and taking responsibilities when flexibility was needed," and "the personalization of problems" were addressed as barriers by team members.

One of the "organization-related barriers" was strict hierarchy, and the other one was staffing problems. Although participants talked about the need of hierarchy in a positive way, they also emphasized strict and vertical hierarchy as a barrier for effective teamwork.

...Hierarchy is not a negative thing in fact, but if it causes pressure and fear, it blocks productive working (RI4).

... Naturally, the boss is the chief of department and after him/her, the chief of ward and other doctors come. Hierarchy goes like that unfortunately... Actually, I believe that it must be a circle. It must be a horizontal management (RI3).

As to staffing problems, there were two main issues. One is staff turnover frequency and the second is lack of staff:

... If there is no continuity among the staff, you cannot mention about the teamwork. People who know each other can produce synergy. A certain time for adaptation is needed. If you are in a 10-person team, and 6–7 persons leave soon and new persons start, you cannot keep going the same way (RI4).

... There was a steady nursing staff in the unit previously, but lately it has changed. It is a vicious circle, one person comes, and you teach her/him and then s/he goes, and another one comes. This causes negative effects on the continuity of care (RI5).

... There are only two psychologists, and one of them is pregnant and will leave the job soon. Only one person will work then. The lack of nurses is a routine problem too. So, it is impossible doing something other than the routines (R9).

Category 3. Suggestions for Effective Teamwork

Participants addressed the need for effective and competent leadership to motivate team members to maintain teamwork. They suggested that leaders needed to be supported to improve their leadership traits. Some quotes emphasizing the importance of capability of the team leader were as follows:

... The attitude of the leader is very important. If the chief of department values teamwork and gives the opportunity to apply, it is very easy to reach the people (R4).

.. If the leader is not competent and does not recognize teamwork, it is impossible to work as a team. In addition, the justice is very important in the team, and the leader should provide this (RII).

...The team leader should understand that every person has different motivational resources and should take some preventive measures to make each person motivate. They also should create a dynamism and cohesion in the team (RI2).

In addition, a democratical atmosphere meant giving everyone the right to speak, for participants. That is why they suggested structured team meetings to facilitate talking to each other and sharing information. Also, a flow of information within the team was a guarantee of improved collaboration.

... Arranging some programs to know each other is important. If we want effective teamwork, we should talk to each other. I must be aware of the other team members and the impact of their work on my tasks and plans... (R8).

...Hierarchy must be loosened. Of course, everybody has different experiences and thoughts, and you can learn from others. Team members should feel free to talk within the team (RI4).

...t must be an environment to have the right to talk equally and freely. I should be able to talk without hesitation... (R9).

...Everybody should feel that they are the part of a team. To be able to provide this and make them feel valuable, team meetings and sharing the information is very important (R3).

Supporting team members financially and giving them opportunities for personal development emerged as another important component to improve teamwork. Participants emphasized that improving personal characteristics, such as respectfulness, tolerance and not showing bias or prejudice, flexibility, active listening, and openness toward criticism may increase collaboration.

.. When something has been criticized, you must listen first without any reaction. You should care about what was said. Reacting before listening causes conflicts (R8).

... Personality is very important. Being egocentric and rebellious or dominant during the work causes conflicts (RI0).

Team members mentioned financial problems as an important factor contributing to the lack of staff and frequent staff turnover. According to participants, if the payments or salaries become more satisfactory, this would help keep team members together in the same work setting.

... Financial problems affect the teamwork negatively. It causes both a rapid personnel change and dissatisfaction with the work. Special compensations, which are added to salaries for the psychiatry personnel, could solve these problems (R8).

DISCUSSION

In this study, mental health team members explained what concepts are important for teamwork from their perspective. Task sharing focusing on patient needs, and identification and mutual acceptance of roles, as the most important features of teamwork, were emphasized topics in our study. In addition, participants emphasized open communication, and democratic and active leadership features.

In the related literature, knowing how team members perceive their own and others' roles are addressed as a very important component in understanding the collaboration necessary for multidisciplinary teamwork. Another important issue is acknowledgment of other members' expertise and roles. Members must be respectful with the responsibilities and boundaries of each discipline, and the atmosphere should allow each discipline to present their own specific skills, understandings, and roles (20, 21).

In this study, barriers to teamwork were factors such as avoiding responsibility, difficulty in getting together, strict hierarchy, devaluing the different roles of team members, personalization of problems, inadequate number and quality of staff, and rapid staff turnover have been stated. Especially, the lack of information and motivation, inexperience, frequent change of employees, lack of quality of staff and some unsolved administrative problems were mentioned as well. On the other hand, there was an acceptance about the possibility of having conflicts within the team as a natural phenomenon.

Like our participants, Kelly (22) states that conflict is a natural phenomenon in which there has been disagreement between individuals who perceive a threat to their needs, interests, and/or concerns. Conflicts can emerge due to relationships and to tasks. Heimer (23) suggested that conflict resolution can be an opportunity for growth and change and a positive outcome. Shaw et al. (24) reported that moderate task conflict and low relationship conflict can lead to good performance. According to participants of this study, if each team member prioritized and focused on patients' needs while they perform their own role, conflicts would be easily solved. This finding coincides with the view that putting the patient at the center reduces tension among the team members (25).

Conflicts usually occur due to interprofessional misunderstandings, different conceptual approaches, different lines of accountability, and imbalances in power, lack of leadership, and lack of communication. Other additional reasons contributing the conflicts are not knowing the professional boundaries, ineffective assertion, psychological unsafety, lack of situational awareness, and the personality traits of members and the overlaps and conflicts in roles. Therefore, improving a number of qualifications such as working together, taking responsibility, coping with anxiety, controlling their emotions, and being trustworthy is very important in maintaining successful teamwork (26-30).

The other main concept in this study was hierarchy. Almost all the professionals mentioned hierarchy. Hierarchy is a structure that exists in almost all health teams, and physicians are usually supposed to manage the team (I4). The participants accepted the hierarchical structure, and it was seen that management of the treatment program by the physician was acceptable. On the other hand, it was emphasized that there should be no rigid hierarchy and authoritarian attitudes of the team leaders. Singh (28) states that such attitudes lead to hostility and aggression, as well as obedience. Therefore, in a rigid hierarchical structure, it can be difficult to develop motivation, spiritual pleasure, and creativity. Some authors suggest that hierarchy reduces success in achieving group cohesion, and in particular, it causes inef-

fective communication between nurses and physicians (31, 32). However, in a hierarchical structure, democratic communication and balanced power relations in the team and teamwork can be adversely affected. In fact, the "bottom-line hierarchy" in which there has been a decision maker is proposed, as a well the functioning structure to enable each member to understand his or her responsibilities, resolve conflicts, and make tough decisions. Hence, although the team-as-a-whole concensual and democratic form of decision making is a good mode of operation, a bottom-line hierarchy with a designated decision maker is vital to ensure that individual professional responsibility is understood, the conflicts are resolved, and difficult decisions are made (28).

As solutions, participants made suggestions that would make communication more clear among the team members to provide effective teamwork. Written or oral communication and team meetings that provide sharing of the information in a democratic milieu were suggested as the tools to solve problems most easily. In this study, regular team meetings, active listening, and non-critical and empathic communication were emphasized to ensure functional communication. In the literature, for the team to be functional, it is stated that it is necessary to create new and professional interaction patterns, to accept changes in authority and status, and to develop conflict resolution and decision making skills (1, 7, 10, 33). To achieve that training programs should be planned in such a way that health professionals can learn from each other and with each other. The structured communication methods such as debriefing, assertive language, critical language, common language, closed communication loops, active listening, and callouts can be used in those programs. In addition, training on assertiveness and mutual trust has been suggested to reduce the negative effect of hierarchy as well (19, 21, 31).

Qualitative description is especially suitable for obtaining straight and largely unvarnished answers to questions of special. The reasons for particular types of behavior can only be understood when it is observed, and people are asked about it (33, 34). Using in-depth interviews in this study provided the opportunity to reveal novel information on what is defined and what is problematic for teamwork to mental health professionals. Findings revealed that definitions have some conceptual differences, even if they are named the same way. In this paper, we suggested a descriptive analytic model in viewing the possible reasons of the teamwork failure. Often when teamwork fails, we feel lost when assessing the reasons of its failure. As Onyett and Campling (10) stated, as we become more sophisticated about the nature of teamwork, it is important that we continue to aspire to this rigor; otherwise we will not be in a position to assess accurately whether we are achieving effective teamwork or not.

A limitation to this study is that the findings may reflect the perspectives of mental health professionals who work in the inpatient hospital setting; mental health professionals who work with outpatients or in the community setting may have different perceptions of teamwork.

In conclusion, we saw that mental health team members had developed their own teamwork perspective and personal style according to work conditions at where and when they had started to work. This finding was consistent with other studies and supported that due to "little formal training on teamwork in undergraduate or postgraduate health professional education, teamwork skills are largely learned 'on-the-job'" (35). Our suggestion for achieving effective teamwork is that it should be taught during undergraduate education and be continuously developed later in working life. In related publications, it is stated that the training programs increase the effectiveness of the team, and interdisciplinary training about communication and teamwork is useful for improving safety culture in health care settings (19, 21, 23).

Implication for Practice

Maintaining teamwork effectively in the mental health field is crucial to achieve positive outcomes. In this era, technology is changing the health care setting and the provision of health care, but we think that even in these advanced technological and digital environments, teamwork directly affects the course of patients' recovery process. Understanding subjective meanings and communalizing them is useful in preventing possible failures.

Thus, the teams who want to achieve an effective teamwork should start with sharing the meaning. Making constant efforts to create a culture that the team members will enable them to reach common understanding with related meanings is crucial.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Verbal informed consent was obtained from health professionals who participated in this study.

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Original Article

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Leukocytoclastic Vasculitis: A Retrospective Analysis of 57 Cases

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BACKGROUND/AIMS
Cutaneous small vessel vasculitis (CSVV) is a small vessel vasculitis affecting the skin primarily, but may be associated with larger systemic vasculitis or extra cutaneous involvement. The clinical hallmark is palpable purpura usually involving the lower extremities. Although CSVV can be induced by drugs, infections, connective tissue diseases, and malignancies, it can also be idiopathic. The aim of the present study was to analyze patients with cutaneous leukocytoclastic vasculitis (LCV) to determine disease characteristics.

MATERIALS and METHODS
In this retrospective study, the records of 57 patients with LCV from 2013 to 2017 managed at the Department of Dermatology were reviewed. A detailed evaluation of the data was done to determine demographic characteristics, etiological factors, clinical signs and symptoms, and treatment options.

RESULTS
The study included 39 female and 18 male patients. The median age of the patients was 55 years. The majority of patients (46, 80.7%) were classified as CSVV. Almost half of the cases (25, 43.9%) were idiopathic, but the most common cause was simultaneous infection and drug usage (12, 21%). The most common cutaneous manifestation was palpable purpura (21, 36.8%) involving the lower extremities (40, 70.2%). The most common extra cutaneous manifestation was joint involvement presenting as arthritis and/or arthralgia (15, 26.3%). The most frequent laboratory abnormality was an elevated C-reactive protein (40, 70.2%).

CONCLUSION
In clinical practice, it is important to keep in mind that although LCV is usually confined to the blood vessels of the skin, a detailed evaluation of the patients is required to detect the underlying causes and systemic involvement.

Keywords: Leukocytoclastic vasculitis, small vessel vasculitis, vasculitis

INTRODUCTION

Vasculitides are a spectrum of diseases with a wide variety of clinical manifestations characterized by a specific inflammation of the blood vessels. The specific inflammation leads to destruction and subsequent hemorrhagic features (1). These conditions may be confined only to the skin or to a lesser extent may be a cutaneous sign of a systemic vasculitic syndrome which is also associated with multiple extracutaneous end organ involvements.

Over the years, various criteria and nomenclature systems have been developed to classify vasculitic syndromes. Unfortunately, there is no ideal system for the accurate classification of vasculitides. The two main classification systems in use are the American College of Rheumatology classification criteria and the revised Chapel Hill Consensus Conference nomenclature system (2, 3). In dermatology practice, it is more useful to classify cutaneous vasculitides based on involved vessel-size predominance (1). Vasculitis can be classified according to the following diameter of the involved vessel: (1) large vessels, (2) medium-sized vessels, and (3) small vessels including arterioles, capillaries, and specifically postcapillary venules (1).

The new name for a group of small vessel vasculitides, formerly called leukocytoclastic vasculitis (LCV), has been proposed to be cutaneous small vessel vasculitis (CSVV). LCV has been accepted as the name of a histological term which

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defines perivascular inflammatory infiltrate consisting of mainly neutrophils, fibrinoid necrosis, swelling of endothelial cells, and erythrocyte extravasation in the postcapillary venules (1). When vasculitis is idiopathic, it is called primary CSVV (4). There are several CSVV subtypes including immunoglobulin A vasculitis (Henoch-Schönlein purpura, HSP), urticarial vasculitis, and cryoglobulinemic vasculitis (4). Furthermore, the small vessel vasculitides are subdivided into antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis which can involve not only small-sized vessels but also medium-sized vessels. The ANCA-associated vasculitides include microscopic polyangiitis, Churg-Strauss syndrome, and granulomatosis with polyangiitis (formerly called Wegener's granulomatosis) (5).

Cutaneous small vessel vasculitis almost always affects the small vessels of the skin, but sometimes extra cutaneous involvement may also occur. Moreover, CSVV findings may appear as cutaneous manifestations of large systemic vasculitides (6). The distinctive clinical feature is the palpable purpura usually involving the lower extremities (4). Although CSVV can be induced by a variety of causes including drugs, infections, connective tissue diseases, and malignancies, it can also be idiopathic (3, 6). The duration of the cutaneous lesions is uncertain. There are several treatment options, but symptomatic measures are enough for most of the cases.

Hence, the aim of the present study was to retrospectively analyze the medical records of patients with cutaneous LCV to determine demographic characteristics, etiological factors, clinical signs and symptoms, and treatment options in 57 patients.

MATERIALS and METHODS

In this cross-sectional study, the records of all patients from 2013 to 2017 with CSVV diagnosed clinically and/or histopathologically at the Department of Dermatology were reviewed. Data were collected from the hospital's database system retrospectively. Patients with diseases leading to bleeding diathesis, patients using anticoagulants, pregnant women, and patients who did not want to sign the informed consent form to allow the evaluation of information regarding their medical history were excluded from the study. The study was approved by the institutional ethics committee of Ankara Training and Research Hospital (Approval no:5/2019, Date:25.04.2019). All participants were informed about the study. Written informed consent was obtained from all of the patients.

Demographic characteristics including age and gender, disease history, possible etiological factors, accompanying conditions, and physical and dermatological examinations of all the patients were reviewed. Disease characteristics were evaluated carefully to determine the disease duration, cutaneous and systemic symptoms, etiologies including infections, drug usage, malignancy, connective tissue diseases, and other associated systemic disorders. Treatment modalities were also evaluated.

Laboratory tests and imaging studies were also collected. These include complete blood count, renal and liver function tests, urine analysis, stool for occult blood, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antistreptolysin O titer, antinuclear antibody, ANCA (both cytoplasmic ANCA: anti-proteinase-3 and perinuclear ANCA: anti-myeloperoxidase antibodies), serum complement fractions, cryoglobulin level, rheumatoid factor, human immunodeficiency virus, hepatitis B virus and hepatitis C virus serology, chest X-ray, and abdominal ultrasonography. Two skin biopsies (punch biopsy, 4 mm) were obtained from the lesions with <48-hour duration for routine histopathology and direct immunofluorescence (DIF). The histopathological confirmation of cutaneous LCV was made by the presence of a perivascular neutrophil-dominant inflammatory infiltrate, leukocytoclasia, fibrinoid necrosis, and extravasation of red blood cells into the vessel wall (1).

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences, version 16.00 (SPSS Inc.; Chicago, IL, USA). Normality of the data was tested. Continuous variables were expressed as mean ± standard deviation, if they had a normal distribution or otherwise, and as median and minimum–maximum. Categorical variables were expressed as number (percentage). Chi-square test or Fisher's exact test was used to analyze categorical variables. Fisher's exact test was used when one or more cell counts were <5. A p value <0.05 was considered as statistically significant.

RESULTS

A total of 57 patients were included in the study. There were 39 (68.4%) female and 18 (31.6%) male patients. The female-to-male ratio was 2.17. The median age of the patients was 55 (14–86) years. The median duration of the disease was 14 (2–120) days.

After all the patients were classified based on clinical findings and laboratory assessments, it was found that the majority of patients (46, 80.7%) had CSVV. This is a diagnosis of exclusion which can only be made after ruling out all other possibilities. The distribution of patients with small vessel vasculitides is presented in Table 1. The etiological factors and associated conditions in our patients are shown in Table 2. In most of the patients (24, 42%), the etiological cause could not be identified, and they were classified as primary CSVV.

TABLE 1. The distribution of patients with small vessel vasculitides

Small vessel vasculitides	Patients (n)
Cutaneous small vessel vasculitis	46 (80.7%)
Primary CSVV	24 (42%)
Secondary CSVV	22 (38.6%)
Subtypes of CSVV	
Henoch-Schönlein purpura	4 (7%)
Urticarial vasculitis	4 (7%)
Cryoglobulinemic vasculitis	1 (1.8%)
ANCA-associated vasculitis	
Granulomatosis with polyangiitis	1 (1.8%)
c-ANCA vasculitis, not otherwise specified	1 (1.8%)

ANCA: antineutrophil cytoplasmic antibody; c-ANCA: cytoplasmic antineutrophil cytoplasmic antibody; CSVV: cutaneous small vessel vasculitis

The cutaneous symptoms and signs of LCV in our study group are presented in Table 3. Cutaneous lesions in 26 (45.6%) patients were asymptomatic, but 18 (31.6%) patients had pruritus, 10 (17.6%) patients had pain associated with the lesions, and 10 (17.6%) patients had burning sensation. Cutaneous lesions involved the lower extremities in 70.2% (40/57) of the patients. Moreover, 22 (38.6%) patients had cutaneous lesions involving only the lower extremities. There were also 13 (22.2%) patients with upper extremity lesions, 10 (17.5%) patients with truncal lesions, and 1 (1.8%) patient with mucosal lesions. Twenty (35.1%) patients had generalized cutaneous lesions.

Extra cutaneous involvement (Table 4) was observed in 19 (33.3%) patients. The most common extra cutaneous manifestation was joint involvement. In 15 cases, arthralgia was found in 12 patients, and arthritis was found in 3 patients (mostly involving the knee). Systemic involvement was detected in approximately one-third of the patients. Joint involvement manifests itself as arthritis and/or arthralgia. Gastrointestinal involvement results in abdominal pain and/or occult blood positivity. Renal involvement causes hematuria and/or proteinuria. Joint involvement was found in 15 (26.3%) patients, gastrointestinal involvement was found in 9 (15.7%) patients, and renal involvement was found in 12 (21%) patients. Patients with renal involvement were consulted to the nephrology department for further evaluation. A 24-hour urine analysis revealed non-nephrotic range proteinuria. Therefore, renal biopsy was not performed, and regular follow-up was scheduled. The investigative profile of the patients is presented in Table 5. The most frequent three laboratory abnormalities were an elevated CRP (40 patients, 70.2%), elevated ESR (33 patients, 57.9%), and anemia (24 patients, 42.1%). There is no relationship between high ESR, presence of leukocytosis, high CRP, and systemic involvement (p=0.569, p=0.095, p=0.370).

TABLE 2. Etiology and associated conditions of small vessel vasculitides

Etiology or association	Patients (n)
Idiopathic	25 (43.9%)
Drug-induced	10 (17.5%)
Infection	8 (14%)
Drug and infection	12 (21%)
Connective tissue diseases (rheumatoid arthritis, dermatomyositis)	7 (12.3%)
Malignancy (solid/hematologic)	4 (3/1) (7%)

*Each patient may be listed in more than 1 category

TABLE 3. Cutaneous manifestations of vasculitis

Cutaneous manifestations	Patients (n)
Palpable purpura	21 (36.8%)
Non-palpable purpura	18 (31.6%)
Ulcers	12 (21%)
Urticarial lesions	2 (3.5%)
Vesiculobullous lesions	2 (3.5%)
Nodules	1 (1.8%)
Livedo reticularis	1 (1.8%)

Two skin biopsies for routine histopathology and DIF examination were performed in 49 (85.9%) patients. Histopathological examination of these patients revealed LCV in 45 (91.8%) patients and nonspecific findings in 4 (8.2%) patients. DIF examination was positive in 30 (61.3%) patients. The most common deposit positivity was for C3 alone in 15 (30.61%) patients, followed by IgM and C3 in 9 (18.3%) patients, IgA in 4 (8.16%) patients, and IgG, IgM, and C3 in 2 (4.1%) patients.

Conventional therapeutic approach for the management of patients with CSVV was symptomatic, such as follow-up, elevation of extremities, application of topical corticosteroids, and/or systemic antihistamines. These first-line treatment options were used in 47 (82.5%) patients. A specific treatment was initiated in 10 (17.5%) patients, mainly for patients with a longer duration of CSVV and more severe clinical manifestations. Four (7%) patients received systemic steroids, 3 (5.3%) patients received colchicine, 2 (3.5%) patients received dapsone, and 1 (1.8%) patient received azathioprine therapy.

DISCUSSION

Leukocytoclastic vasculitis refers to the new name for a histopathological description that is neutrophilic inflammation of the postcapillary venules (1). A wide variety of clinical entities can lead to LCV in the skin. In this retrospective, cross-sectional study, we report findings in 57 patients with LCV.

TABLE 4. Extra cutaneous associations of small vessel vasculitides in the patients

Extra cutaneous manifestations	Patients (n)
None	38 (66.7%)
Arthralgia	12 (21%)
Arthritis	3 (5.3%)
Abdominal pain	4 (7%)
Fever	4 (7%)
Fatigue	4 (7%)
Nausea and vomiting	2 (3.5%)
Weight loss	1 (1.8)

TABLE 5. Laboratory evaluation of the patients

Test	Patients (n)
Elevated CRP (>0.8 mg/dL)	40 (70.2%)
Elevated ESR (20 mm/h)	33 (57.9%)
Anemia (Hb <12 g/dL)	24 (42.1%)
Leukocytosis (>10000 mm^3)	16 (28.1%)
Elevated ASO (>200 IU/mL)	12 (21%)
Hematuria	12 (21%)
Elevated liver function tests (ALT >40 U/L; AST >33 U/L)	11 (19.3%)
Rheumatoid factor (>20 IU/mL)	8 (14%)
ANA positivity	8 (14%)
Hypocomplementemia (C3 79–152 mg/dL, C4 16–38 mg/dL)	6 (10.5%)
Fecal occult blood	5 (8.8%)

ALT: alanine aminotransferase; ANA: antinuclear antibody; ASO: antistreptolysin O; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin

In the present study, the median age of patients with LCV was 55 years, and the female-to-male ratio was 2.17. Chua et al. (7) also conducted a retrospective analysis of cutaneous vasculitis and reported that the female-to-male ratio is 2 in their study group. However, some other studies have found that the disorder was more common in men or equal in both sexes (8, 9).

Primary CSVV represented the majority of patients (42%) with cutaneous LCV in our study, which is similar to the 40.7% incidence reported by Blanco et al. and 36.8% incidence reported by Al-Mutairi (6, 10). Tai et al. (11) evaluated 93 adult patients and reported that the most common small vessel vasculitis is cutaneous LCV (68 patients, 73.2%) in their study group, followed by HSP (11 patients, 11.8%), microscopic polyangiitis (5 patients, 5.4%), septic vasculitis (4 patients, 4.3%), Wegener's granulomatosis (2 patients, 2.2%), Churg-Strauss syndrome (1 patient, 1.1%), and essential cryoglobulinemic vasculitis (1 patient, 1.1%), respectively. Blanco et al. (6) conducted a study involving 303 patients consisting of 172 adults and 131 children. The most common small vessel vasculitis in the study population was HSP (155 patients, 51.6%), followed by cutaneous LCV (84 patients, 27.7%). The other diagnoses were polyarteritis nodosa (17 patients, 5.6%), essential mixed cryoglobulinemia (11 patients, 3.6%), Wegener's granulomatosis (4 patients, 1.3%), and Churg-Strauss syndrome (2 patients, 0.6%), respectively. In our study of 57 patients, 46 (80.7%) patients had CSVV (24 primary and 22 secondary), 4 (7%) patients had HSP, 4 (7%) patients had urticarial vasculitis, 2 (3.5%) patients had ANCA vasculitis, and 1 (1.8%) patient had cryoglobulinemic vasculitis. The difference in the incidence of the types of vasculitides in several studies might be explained by the use of different classification systems, such as the American College of Rheumatology criteria and the revised Chapel Hill Congress Conference nomenclature system that had variable definitions for vasculitides and vasculitic syndromes (2, 3). Moreover, the age range of the patients included in the studies might affect the incidence of vasculitides. HSP cases appeared to be more common in the studies that included a higher number of patients belonging to the pediatric population (6).

Although almost half of the cases with CSVV are idiopathic, a detailed investigation for any underlying causes or associations is essential (1). CSVV may be caused by infections (15%–20%), autoimmune connective tissue diseases or inflammatory conditions (15%–20%), drugs (10%–15%), and hematologic or solid malignancies (5%) (1, 12). In our study group, the main cause was the presence of simultaneous drug usage and infection (12 patients, 21%). The second and third most common causes were drug usage alone (10 patients, 17.5%) and having an infection alone (8 patients, 14%) respectively. Drug- and infection-induced vasculitis was observed more frequently in our study group than in previous studies (6, 8, 13). This may be due to the fact that patients applying to a tertiary institution (probably after primary practices) were more likely to be complicated by an infection and consequently had increased use of medication.

Palpable purpura (21 patients, 36.8%) involving the lower extremities (40 patients, 70.2%) was the most commonly observed cutaneous manifestation of LCV in the present study, in accordance with the previous studies (14, 15). It was assumed as the most sensitive diagnostic sign for cutaneous LCV (16). Lesions may cause pruritus, pain, and burning as mentioned in our study (4).

Leukocytoclastic vasculitis primarily involves the small caliber blood vessels of the skin, but in approximately 50% of the patients, the small vessels of the joints, gastrointestinal tract, kidneys, muscles, lungs, and peripheral nerves could be involved, leading to multisystem organ involvement (17). We observed systemic involvement in approximately one-third of our patients. Arthralgia and arthritis, namely joint involvement, were the most frequent extra cutaneous findings of our study. The other frequent extra cutaneous findings were renal and gastrointestinal involvements, respectively. In line with the findings of our study, several studies evaluating the sites of involvement in LCV reported that the most frequent non-cutaneous finding was joint involvement (14, 18-20).

In the present study, the most frequent laboratory abnormality was an elevated CRP level, followed by elevated ESR and anemia. However, there is no relationship between high ESR, presence of leukocytosis, high CRP, and presence of systemic involvement. Most of the studies revealed that ESR was the most frequent pathological laboratory finding (11, 18, 20), whereas some of them also indicated a relationship between elevated ESR and systemic involvement (14).

The natural course of LCV is usually benign and self-limiting, so symptomatic measures are the first-line treatment option. Follow-up, topical corticosteroids, and systemic antihistamines are sufficient to control the symptoms in most of the cases. If the disease is persistent and/or recurrent, drugs, such as dapsone, colchicine, and pentoxifylline, are used. If there is a moderate-to-severe disease accompanied by vesicles, ulcers, and nodules, systemic steroids and immunosuppressive drugs, such as azathioprine, methotrexate, cyclosporine, and cyclophosphamide, are given (10). In our study group, first-line treatment options were enough to control the symptoms of 47 (82.5%) patients. A total of 5 patients with a longer disease duration and more severe clinical manifestations had received immunosuppressive treatment. Four (7%) patients received systemic steroids, 1 (1.8%) patient received azathioprine therapy, 3 (5.3%) patients received colchicine, and 2 (3.5%) patients received dapsone. Cakiter et al. (18) evaluated treatment options in 75 patients and reported that symptomatic treatment is enough in the management of 46 (61.3%) patients, whereas the rest of the patients needed specific treatment options, such as systemic steroids (12 patients, 16%), colchicine (9 patients, 12%), dapsone (7 patients, 9.3%), and azathioprine (1 patient, 1.3%). Bouiller et al. (21) studied 112 patients with LCV and reported that a specific treatment is initiated in 41 (36.6%) patients and those were the secondary cases with an underlying cause. In their study, the most commonly preferred treatment options were prednisone (70.7%), hydroxychloroquine (14.6%), and colchicine (12.2%). LCV treatment is initiated based on the severity of disease and end organ involvement. Therefore, the frequency of the use of treatment options varies between studies, but aggressive treatment is not necessary most of the time because of the benign course of the disease.

In conclusion, LCV is a clinicopathological term gathering several vasculitis entities together. LCV affected patients with a median age of 55 years, and there was a female preponderance in the present study. LCV classically presented as symmetric palpable purpura of the lower extremities. The disease was

frequently idiopathic, but the most commonly identified underlying cause was the presence of simultaneous drug usage and infection. An elevated CRP was the most common laboratory finding. Symptomatic treatment options are sufficient for most of the cases due to the benign, self-limiting course of the disease. In clinical practice, it is important to keep in mind that although LCV is usually confined to the blood vessels of the skin, a detailed evaluation of the patients is required to detect the underlying causes and systemic involvement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Training and Research Hospital (Approval no:5/2019, Date:25.04.2019).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Original Article

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The Interaction between ESRRA and PTH Gene Methylation and Body Mass Index in Post-Menopausal Cases

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BACKGROUND/AIMS
Post-menopausal and hormone-related diseases are the biggest problems for women on which genetic and environmental factors have an effect.

MATERIALS and METHODS
In this study, the methylation status of ESRRA (Estrogen Related Receptor Alpha) and PTH (Parathyroid Hormone) promoters was analyzed in 30 pre-menopausal and 35 post-menopausal women by using MS-HRM (Methylation Sensitive-High Resolution Melting). The height (cm) and weight (kg) of each participant were measured. The statistical analyses were performed and their associations with patient characteristics were evaluated by Pearson's chi-squared test, two-tailed Fisher's exact test, and Mann–Whitney U test ($p<0.05$).

RESULTS
The PTH gene was methylated in four post-menopausal cases (11.4%) and unmethylated in 31 cases (88.6%). The ESRRA gene was methylated in six post-menopausal cases (17.1%) and unmethylated in 29 cases (82.9%). There were no significant differences between post-menopause and PTH methylation ($p>0.005$); however, a statistically significant association was detected between post-menopause and unmethylation of ESRRA ($p=0.040$). Also, no significant differences were detected between body mass index (BMI) and methylation parameters.

CONCLUSION
Estrogen plays a significant role in the regulation of skeletal homeostasis, lipid and carbohydrate metabolism, and the central nervous system. Researchers showed the relationship among ESRRA, BMI, and fat percentage in animal models. However, we did not find any statistically significant relationship between ESRRA methylation and BMI in post-menopausal women. To the best of our knowledge, this is the first study that investigates the relationship between the methylation of PTH and ESRRA genes, and BMI in post-menopausal cases. Future epigenetic studies will help to clarify potential effects of gene methylation in post-menopause.

Keywords: Body mass index, estrogen related receptor alpha, methylation, parathyroid hormone, post-menopause

INTRODUCTION

Estrogen is the important hormonal regulator of female reproductive functions that plays a significant role in the regulation of skeletal homeostasis, lipid and carbohydrate metabolism, electrolyte balance, skin physiology, cardiovascular system, and the central nervous system (1). Genetic and environmental factors have an effect on post-menopausal and hormone-related diseases (2). Lane and colleagues identified the genetic background of menstrual cycle and showed the role of the RANKL/RANK/OPG pathway in timing of the menstrual cycle (3). Genetic, demographic, and reproductive characteristics, lifestyle, and body weight are associated with the timing of menopause (4). Recent studies have focused on the relationship between body mass index (BMI) and the timing of age at menopause, but the results are still inconsistent. For example, Hardy and colleagues noted that an earlier age at menopause is associated with underweight (5). On the other hand, Dratva and colleagues concluded that a higher BMI is associated with earlier menopause (6) but in contrast to this, other researchers noted that there is no association between BMI and menopause timing (7).

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BMI has been widely used as a screening tool for obesity, but it only represents a proxy measure of body fat mass, because it does not take into account differences in genetic or epigenetic factors. BMI was compared between pre-menopausal and post-menopausal women in cross-sectional studies and significant differences were detected between pre-menopausal and post-menopausal women. Previous studies used different parameters like age, energy intake, sex hormone-binding globulin levels, and genetic polymorphisms to be able to show the interaction between obesity or increased BMI and menopause.

Until now, all of the studies have tried to show the interaction between genetic polymorphisms and obesity, menopause, or age of menopause (8). Few studies have been published which show obesity-related variation in DNA methylation, which were related with global methylation or candidate gene approaches (9).

To better understand the interaction of menopause and BMI, we compared associations between BMI and methylation of ESRRA (Estrogen Related Receptor Alpha) and PTH (Parathyroid Hormone) in pre- and post-menopausal cases.

MATERIALS and METHODS

For this study, 35 post-menopausal and 30 pre-menopausal women were recruited. Written informed consent was obtained from all of the subjects. The study was performed in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the Near East University (YDU/2016/42-353). The inclusion criterion for the study was: all post-menopausal ladies (menopause for >1 year) and exclusion criteria were: women with un-natural menopause, women who took medications such as anxiolytics, anti-depressants, and exogenous hormones, women who have serious disease or mental retardation, smoking, alcohol usage, and women who have a weight loss therapy, food allergies, heart disease history, insulin-dependent diabetes, type 2 diabetes, kidney disease or liver disease.

Genomic DNA was extracted from blood samples according to the Qiagane AllPrep DNA/RNA/Protein isolation kit and its quantity was measured using a NanoDrop ND-1000 Spectrophotometer (Thermo Fisher Scientific).

Anthropometry

The anthropometric data included body weight, height, and BMI (weight/height^2). Body weight was measured to the nearest 0.1 kg with subjects in a bathing suit following an overnight fast and without shoes, using a calibrated scale. Waist circumference was measured at the midpoint between the lowest rib and the top of the iliac crest using a non-elastic tape. This measurement was performed by a single evaluator.

Determination of PTH and ESRRA Methylation Status

An EpiTect Bisulfite kit (Qiagen, Manchester, UK) was used for the bisulfite modification reaction and 1.3 μg DNA was used for the bisulfite treatment reaction according to the manufacturers' protocol. After conversion, converted DNA was eluted to a final concentration of 30 ng/μl. For methylated and unmethylated control, a DNA EpiTect Control DNA Set (Qiagen, Manchester, UK, Cat No./ID: 59568) was used. Methylation of PTH and ESRRA promoters was analyzed in Rotor Gene Q (Qiagen, Manchester, UK) for MS-HRM and primers were designed according to the EpiTect® HRM™ PCR Handbook (Qiagen, Manchester, UK). The comparable amounts of template genomic DNA for all samples which results in cycle threshold (CT) values below 30 and differing by no more than 3 CT values have been used.

Statistical Analysis

The statistical analyses were performed and their associations with patient characteristics were evaluated by Pearson's chi-squared test, Fisher's exact test, or Mann–Whitney U test, where appropriate. Calculations were performed using Statistical Package for the Social Sciences 16.0 software (SPSS Inc.; Chicago, IL, USA), with a statistical significance of $p<0.05$.

RESULTS

Methylation data were only available in whole blood. The mean age of 30 pre-menopausal patients was 33.5 years (mean ± standard deviation, 33.5±6.9) and that of the post-menopausal patients was 56.7 (mean±standard deviation, 56.7±4.9).

PTH Methylation and BMI Interaction

In the study group, the PTH promoter was methylated in four (11.4%) post-menopausal women and unmethylated in 31 (86.6%) of the pre-menopausal women (Table 1).

In the control group, 8 (26.7%) of the samples were methylated and 22 (73.3%) of the samples were unmethylated (Table 1). There is no statistically significant association between menopause and methylation of the PTH promoter ($p>0.05$) (Figure 1). Also, no significant associations between BMI and methylation parameters were detected ($p>0.05$).

TABLE 1. BMI and methylation status of ESSRA and PTH in post and pre-menopausal cases

	BMI ($\bar{x}$±SD)	p+	Pre-menopause n (%)	Post-menopause n (%)	p*
PTH-methylated	25.8±2.5	>0.05	8 (26.7%)	4 (11.4%)	>0.05
PTH-unmethylated	25.1±3.5		22 (73.3%)	31 (86.6%)	
ESRRA-methylated	24.8±2.9	>0.05	12 (40%)	6 (17.1%)	0.040
ESRRA-unmethylated	25.5±3.5		18 (60%)	29 (82.9%)	

* Chi-squared test
\+ Mann–Whitney U test
BMI: body mass index; SD: standard deviation; PTH: Parathyroid Hormone; ESRRA: Estrogen Related Receptor Alpha

ESRRA Methylation and BMI Interaction

The ESSRA gene was detected to be methylated in six (17.1%) post-menopausal cases and unmethylated in 29 (82.9%) post-menopausal cases. In the control group, the ESRRA gene was methylated in 12 (40%) cases and unmethylated in 18 (60%) cases (Figure 2). There were statistically significant association between post-menopause and the methylation status of ESRRA (p=0.040). Also, no significant associations between BMI and methylation parameters were detected (p>0.05) (Table I).

DISCUSSION

The level of estrogen decreased during the menopause and this causes different physiological and hormonal problems in women. The epigenetic control of the estrogen receptors (ER) regulates the expression of ER target genes and estrogen-regulated processes (10). The relationship between ESRRA and BMI or fat percentage was studied by several researchers (11). Mueller and colleagues showed the obese phenotype in the Esrra knockout mouse (12) and concluded that ESRRA plays an important role in energy metabolism (12).

The first BMI-related epigenetic study was carried out by Boyne and colleagues and they did not find significant associations between adiposity and Alu methylation (13). They also tried to show the association between endogenous sex hormone exposure and LINE-1 and Alu methylation in post-menopausal women, and they showed the significant association between LINE-1 methylation estradiol and estrone usage (13). They concluded that the usage of estrogen was associated with repetitive element DNA methylation in post-menopausal women (14). Jintaridith and colleagues showed association between Alu hypomethylation and advanced age and lower bone mass density in post-menopausal cases (15).

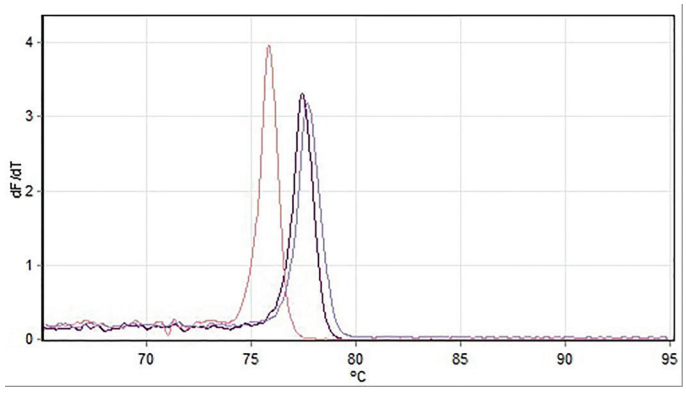

FIGURE 1. Methylated PTH patient.PTH unmethylated control is shown in red, and methylated control is shown in blue. Patient number 25 was methylated

Various genetic and epigenetic studies have been carried out in post-menopausal cases. Epigenetic regulation of post-menopausal status is an interesting field and researchers have tried to show interactions between DNA methylation and BMI, and osteoporosis and age of menopause. Researchers showed the relationship among ESRRA, body mass index (BMI), and fat percentage in animal models.

In this study, we analyzed PTH and ESRRA methylation in post-menopausal cases and tried to find out their interaction with BMI. There were no significant association between post-menopause and PTH methylation (p>0.005), but a statistically significant association was detected between post-menopause and ESRRA methylation status (p=0.040). Also, no significant differences were detected between BMI and methylation parameters.

To the best of our knowledge, this is the first study investigating the relationship between methylation of PTH and ESRRA genes and BMI in post-menopause. Future epigenetic studies will help to clarify potential effects of gene methylation in post-menopause.

In conclusion, the present study demonstrates that ESRRA unmethylation is associated with post-menopause but there is no association between PTH and post-menopausal cases. There is no association detected between methylation of ESRRA and PTH and BMI. This study is the first epigenetic study that investigates the ESRRA and PTH methylation in post-menopausal cases.

Although the limited number of sample size in our study and lack of epigenetic studies in this field prove our results crucial, our results showed magnitude of the epigenetic profile of Turkish Cypriot post-menopausal women.

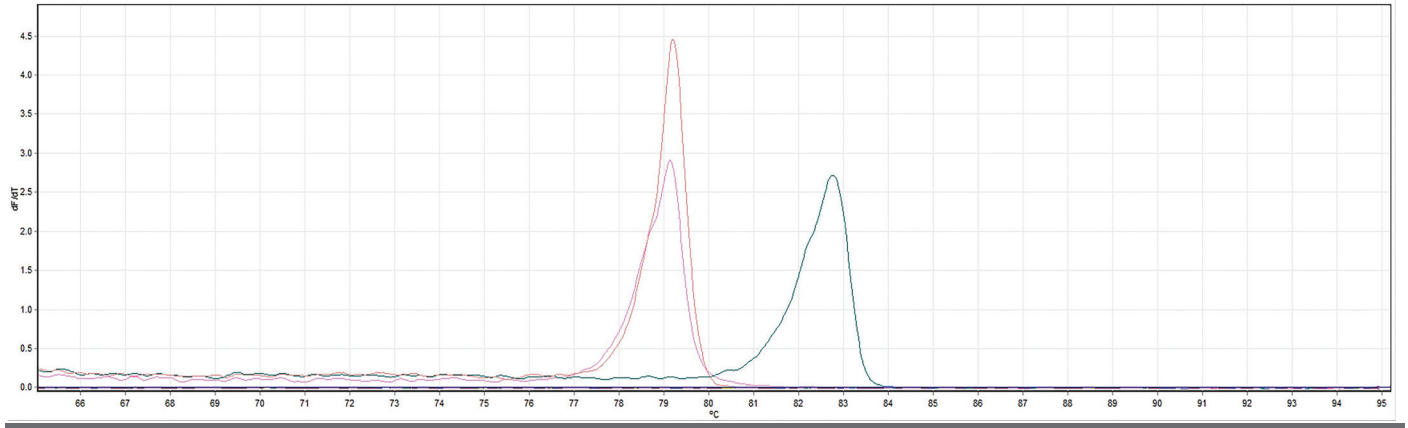

FIGURE 2. Unmethylated ESRRA patient. ESRRA unmethylated control is shown in red, and methylated control is shown in green. Patient number 49 was unmethylated

Ethics Committee Approval: The study was performed in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of the Near East University (YDU/2016/42-353).

Informed Consent: Written informed consent was obtained from all of the subjects.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – R.K.; Design – R.K.; Designed – P.T., R.K.; Supervision – R.K., O.T.; Resource – R.K.; Materials - R.K.; Data Collection and/or Processing – R.K., M.A.; Analysis and/or Interpretation – O.T. Literature Search – R.K.; Writing – R.K.; Critical Reviews – R.K., O.T.

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

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Viral Seroprevalence in Tinnitus

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BACKGROUND/AIMS
Tinnitus is a common medical problem that disrupts patient comfort. The majority of the reasons accused in the etiology of tinnitus are unknown. The aim of the present study was to determine the serology of the viruses, especially antibodies, related to Herpes Simpleks Virus (HSV), Varisella Zoster Virus (VZV), Cytomegalovius (CMV), Ebstein Barr Virus (EBV), measles, mumps, rubella, toxoplasma, and parvovirus B19 in patients with tinnitus. We think that viral infections may be an important factor in tinnitus.

MATERIAL and METHODS
Enzyme linked immunosorbent assay (ELISA) tests were done for both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies. For statistical evaluation, the SPSS 15 program was used.

RESULTS
We found HSV-1 IgM/IgG and anti-VZV IgM/IgG seropositivity as 0% and 80% and 0% and 90%, respectively. Anti-CMV IgM and CMV IgG antibodies were detected as 0% and 100%, respectively, and Ebstein Barr Virus Viral Capsid Antigen (EBV VCA) IgM, EBV VCA IgG, Ebstein Barr Virus Nuclear Antigen (EBNA) IgM, and EBNA IgG seropositivity as 0%, 90%, 0%, and 95%, respectively. Anti-rubella IgM and IgG antibodies were detected as 0% and 90%, respectively. We found anti-measles IgM/IgG and anti-mumps IgM/IgG seropositivity as 2.5% and 80% and 2.5% and 87.5%, respectively. We determined anti-toxoplasma IgM/IgG antibodies as 0% and 40%, respectively, and parvovirus B19 IgM/IgG seropositivity as 5% and 95%, respectively.

CONCLUSION
Infections may be a cause for tinnitus. When our results were compared with both international and national studies for parvovirus serology, higher rates for parvovirus B19 seropositivity have been observed in patients with tinnitus in our study. More comprehensive and more patients included in the studies may contribute to the literature.

Keywords: Parvovirus B19, seroprevalence, tinnitus, viral infections

INTRODUCTION

Tinnitus is a common medical problem that disrupts patient comfort. It is described as a perception of sound in the absence of an external source. In recent studies, the prevalence of tinnitus is estimated to be 10%–15%. Mild to moderate complaints have been reported in 60% of patients, while severe complaints have been seen in 40% of patients (1).

The majority of the reasons accused in the etiology of tinnitus are unknown. Generally, tinnitus can be categorized as continuous, intermittent, or temporary clinically. Continuous tinnitus and intermittent tinnitus are described as chronic tinnitus, whereas temporary tinnitus is considered as an acute episode and does not have a potential for recurrence (2).

The known etiology of tinnitus are peripheral auditory lesions, sudden sensorineural hearing loss, noise exposure or noise-induced hearing loss (most common cause), head or neck trauma, chronic neck or jaw problems, systemic ototoxic therapies, acute or chronic otologic infection, or iatrogenic (surgery) causes. Alternatively, damage or compression of the auditory nerve (e.g., microvascular compression from skull base mass and vestibular schwannoma) can also lead to tinnitus perception. It is emphasized that the face and neck can directly influence the central auditory neural pathways (3).

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In addition, temporomandibular joint disorders; cervical spine disorders including arthritis, cervical spine joint, and intervertebral disk degeneration; fibromyalgia; and whiplash injuries have been linked with tinnitus perception. The accused neural mechanisms include the specific trigeminal nerve and cervical inputs (3).

The majority of infectious agents can cause head and neck inflammation, and some of the viruses cause nerve-related latent infections. The herpesvirus family all cause latent infections in humans. Latency with all herpesviruses in humans is probably associated with frequent subclinical reactivation, which may lead to neuronal inflammation (4-6).

Latency is described as infectious agents, especially viruses, that cause chronic persistent infections by escaping a cell-mediated immune response. A reactivated virus may spread and initiate an epidemic among susceptible contacts, such as Varicella Zoster Virus (VZV). Viral latency can also be seen in the development of several chronic diseases dependent on the immunological response. Examples of latent infection include rubella, cytomegalovirus (CMV), ebstein barr Virus (EBV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), latent Herpes simpleks virus (HSV), VZV, adenovirus, and progressive rubella panencephalitis. Latent viral infections affect the incidence and pathogenesis of acute viral disease in several ways (4).

In the present study, we aimed to determine the serology of the viruses, especially viruses that have latency potential, such as HSV, VZV, CMV, and EBV. Furthermore, anti-measles, anti-mumps, anti-rubella, anti-toxoplasma, and parvovirus B19 antibodies were detected in patients with tinnitus. We think that latent viral infections may cause intermittent reactivation and cause neural inflammation and recently tinnitus.

MATERIAL and METHODS

Patients

The study was conducted between December 2018 and April 2019. Fırat University ethical approval [2019/10 (03); Date 13.06.2019; Approval No: 10 (03)] and informed consent were obtained. Inclusion criteria were as follows:

- No complaints about infectious diseases,
- No chronic metabolic diseases (e.g., malignancies, diabetes, and hypertension),
- No drug use,
- Without defined allergic disorder.

Five cc blood samples were collected, sera were obtained, and ELISA tests (Architect-Abbott, USA) were done for hepatitis B virus surface antigen (HBsAg), hepatitis B virus surface Antibody (anti-HBs), hepatitis C virus antibody (anti-HCV), human immunodeficiency virus antibody (anti-HIV), HSV immunoglobulin (Ig)M, HSV IgG, CMV IgM, CMV IgG, VZV IgM, VZV IgG, ebstein barr virus viral capsid antigen (EBV VCA) IgM, EBV VCA IgG, ebstein barr virus Nuclear Antigen (EBNA- IgM), EBNA IgG, ebstein barr virus aarly antigen (EBV EA) IgM, EBV EA IgG, anti-rubella IgM, anti-rubella IgG, anti-measles IgM, anti-measles IgG, anti-mumps IgM, anti-mumps IgG, parvovirus B19 IgM, parvovirus IgG, toxoplasma IgM, and toxoplasma IgG immediately.

Statistical Analysis

The Statistical Package for the Social Sciences 15 program (SPSS Inc.; Chicago, IL, USA) was used for statistical evaluation.

RESULTS

A total of 40 (28 male and 12 female) patients were included in the study. The mean age of the patients was 51±11 years. The demographic characteristics and results of the patients are presented in Table 1.

We found HSV-1 IgM/IgG and anti-VZV IgM/IgG seropositivity as 0% and 80% and 0% and 90%, respectively. Anti-CMV IgM and CMV IgG antibodies were detected as 0% and 100%, and EBV VCA IgM, EBV VCA IgG, EBNA IgM, and EBNA IgG seropositivity as 0%, 90%, 0%, and 95%, respectively. Anti-rubella IgM and IgG antibodies were detected as 0% and 90%, respectively. We found anti-measles IgM/IgG and anti-mumps IgM/IgG seropositivity as 2.5% and 80% and 2.5% and 87.5%, respectively. We determined anti-toxoplasma IgM/IgG antibodies as 0% and 40%, respectively, and parvovirus B19 IgM/IgG seropositivity as 5% and 95%, respectively. The mean antigen/antibody titers of the positive groups are presented in Table 2.

DISCUSSION

In present study, we evaluated Toxoplasma- Other- Rubella-Cytomegalovirus-Herpes (TORCH), mumps, parvovirus, EBV, and CMV antibodies in patients who have complaints of tinnitus. In our study, we found HSV-1 IgM and IgG seropositivity as 0% and 80%, respectively. In the international literature, HSV-1 mean seroprevalence has been presented as 88.4%–99.2% in those adults (7, 8). In Turkey, there is limited study about HSV serology. In a study from Turkey, anti-herpes simplex IgG and IgM antibodies have been detected as 73.8%–80.0% and 28.6%, respectively (9, 10). Our results were found to be lower than foreign national studies but similar as studies from Turkey. Our lower rates can be related to socioeconomic differences and also to different age groups. In our study, the mean age of the patients was 51 years.

In the present study, we found VZV IgM and IgG seropositivity as 0% and 90%, respectively. In a previous study, varicella seroprevalence has been found to be 97.8% (11). In different ethnic groups, VZV seroprevalence has been reported as 95% among women born in the United Kingdom (UK) and 90% among South Asian women born in Asia (12). In a study from Turkey by Kayın et al. (13), 3570 samples have been tested, and VZV IgM seropositivity and seronegativity have been reported as 7.6% and 89%, respectively. The number of VZV IgG seropositivity and seronegativity has been reported as 72.2% and 23.2%, respectively. In another study, VZV seropositivity rate has been reported as 99.7% in healthcare workers (14). Our results are similar as other foreign literature's results and Cılız's study (14). However, our results are higher than Kayın et al.'s study. The reason can be related to differences in age groups.

We found CMV seropositivity rates for CMV IgM and CMV IgG antibodies as 0% and 100%, respectively. In international stud-

TABLE I. Demographic characteristics and test results

A. Demographic characteristics	
• Male/female, n (%)	28/12 (70/30)
• Mean age (year)	51±11
B. Test values	**Results, n (%)**
• HBsAg positivity	4 (10)
• Anti-HBs positivity	22 (55)
• Anti-HCV positivity	2 (5)
• Anti-HAV IgG positivity	40 (100)
• Anti-HIV positivity	0 (0)
• HSV IgM positivity	0 (0)
• HSV IgG positivity	32 (80)
• CMV IgM positivity	0 (0)
• CMV IgG positivity	40 (100)
• VZV IgM positivity	0 (0)
• VZV IgG positivity	36 (90)
• EBV VCA IgM positivity	0 (0)
• EBV VCA IgG positivity	36 (90)
• EBNA IgM positivity	0 (0)
• EBNA IgG positivity	38 (95)
• Anti-rubella IgM positivity	0 (0)
• Anti-rubella IgG positivity	36 (90)
• Anti-measles IgM positivity	1 (2.5)
• Anti-measles IgG positivity	32 (80)
• Anti-mumps IgM positivity	1 (2.5)
• Anti-mumps IgG positivity	35 (87.5)
• Parvovirus B19 IgM positivity	1 (2.5)
• Parvovirus B19 IgG positivity	38 (95)
• Toxoplasma IgM positivity	0 (0)
• Toxoplasma IgG positivity	16 (40)
• VDRL	0 (0)
• TPHA	0 (0)

HBsAg: Hepatitis B Surface antigen; Anti-HBs: Hepatitis B Surface Antibody; Anti-HCV: Hepatitis C virus Antibody; Anti-HAV IgG: Hepatitis A virus Antibody Immunoglobulin G; Anti-HIV positivity: Human Immunodeficiency Virus Antibody; HSV IgM: Herpes Simpleks Virus Immunoglobulin M; HSV IgG: Herpes Simpleks Virus Immunoglobulin G; CMV IgM: Cytomegalovirus Immunoglobulin M; CMV IgG: Cytomegalovirus Immunoglobulin G; VZV IgM: Varisella zoster virus Immunoglobulin M; VZV IgG: Varisella zoster virus Immunoglobulin G; EBV VCA IgM: Ebstein Barr virus Immunoglobulin M; EBV VCA IgG:Ebstein Barr virus Immunoglobulin G; EBNA IgM:Ebstein Barr Virus Nuclear Antigen Immunoglobulin M; EBNA IgG:Ebstein Barr Virus Nuclear Antigen Immunoglobulin G; VDRL: Veneral Diseases Research Laboratory, TPHA: Treponema Pallidum Hemagglutination Assay

ies, CMV seroprevalence was 49% among White British women, 89% among South Asian UK born women, and 98% among South Asian women born in South Asia (12). In studies from Turkey, anti-cytomegalovirus antibodies were detected as 80.0% in the study group (9). Seropositivity rates of CMV IgM and IgG antibodies were 0.1% and 99.8%, respectively (15). These differences remained after adjusting for socio-demographic factors, vaccination history, and ages.

TABLE 2. Cut-off values, mean antigen/antibody titers, 95% confidence intervals, and minimum–maximum ranges

Antigen/ antibody	Test cut-off value for positivity	Mean positive titers	95% CI	(Min–max) Range
HBsAg	>0.99	1825		(0.06–3297)
Anti-HBs	>9.99	274		(0–1000)
Anti-HCV	>0.99	1.63		(0–1.63)
Anti-HAV IgG	>0.99	9.5		(0–12.05)
HSV IgM	>1	0.30	0.17–0.43	(0.16–0.62)
HSV IgG	>5	45.5	1.3–52.4	(0.34–100)
CMV IgM	>0.85	0.23	0.8–0.38	(0.06–0.56)
CMV IgG	>6	212.7	191–234	(93–250)
VZV IgM	>9	1.6	1.1–2.2	(0.69–2.7)
VZV IgG	>9	16	9.6–23.5	(5.5–940)
EBV VCA IgM	>0.9	0.26	0.4–0.47	(0.07–0.84)
EBV VCA IgG	>1.1	4.35	3.3–5.3	(2.6–5.7)
EBNA IgM	>1	0.21	0.11–0.33	(0.10–0.39)
EBNA IgG	>1	2.04	1.4–2.6	(1.5–3.5)
Anti-rubella IgM	>1	0.16	0.006–0.32	(0.0–0.52)
Anti-rubella IgG	>5	86.2	7.5–165	(1.70–476.4)
Anti-measles IgM	>9	3.08	1.7–4.3	(0.25–11.90)
Anti-measles IgG	>9	21.5	14–29	(2.80–34.9)
Anti-mumps IgM	>9	2.7	1.7–3.6	(0.48–19.70)
Anti-mumps IgG	>9	20.8	13.3–28.2	(4.9–34.7)
Parvovirus B19 IgM	>0.9	0.25	0.18–0.33	(0.20–0.47)
Parvovirus B19 IgG	>2	27	14.5–39.7	(5–43)
Anti-toxoplasma IgM	>1	0.14	0.07–0.22	(0.08–0.34)
Anti-toxoplasma IgG	>1.6	14.8	1.1–3.2	(0.03–24.9)

CI: confidence interval; HBsAg: Hepatitis B Surface antigen; Anti-HBs: Hepatitis B Surface Antibody; Anti-HCV: Hepatitis C virus Antibody; Anti-HAV IgG: Hepatitis A virus Antibody Immunoglobulin G; HSV IgM: Herpes Simpleks Virus Immunoglobulin M; HSV IgG: Herpes Simpleks Virus Immunoglobulin G; CMV IgM: Cytomegalovirus Immunoglobulin M; CMV IgG: Cytomegalovirus Immunoglobulin G; VZV IgM: Varisella zoster virus Immunoglobulin M; VZV IgG: Varisella zoster virus Immunoglobulin G; EBV VCA IgM: Ebstein Barr virus Immunoglobulin M; EBV VCA IgG:Ebstein Barr virus Immunoglobulin G; EBNA IgM:Ebstein Barr Virus Nuclear Antigen Immunoglobulin M; EBNA IgG:Ebstein Barr Virus Nuclear Antigen Immunoglobulin G

We evaluated EBV VCA IgM, EBV VCA IgG, EBNA IgM, and EBNA IgG as 0%, 90%, 0%, and 95%, respectively. EBV seroprevalence has been reported as 94% in a previous literature (12). In a previous study, EBV VCA IgG has been reported as 90% seroprevalence after the age of 26 years (16). In another study, mean EBV seropositivity has been found to be 96.4%–97.9% (11, 17). Our results are similar with the literature.

Anti-rubella IgM and IgG antibodies were detected in our study group and their seropositivity rates were found to be 0% and 90%, respectively. In the international literature, rubella seroprevalence has been reported as 87.6%–90.4% (11, 18). In Turkey, the seropositivity rate of rubella IgG has been found to be 94%–98.8% (9, 15, 18). In a study from our country, 613 pregnant women have been evaluated for rubella antibodies, and rubella IgG seroprevalence

has been found to be 99.5% and IgM antibodies have been found to be 0.3% (19). Our results are similar with the literature.

In our study, we found anti-measles IgM and IgG seropositivity as 2.5% and 80%, respectively. Measles susceptibility was found to be 20% in our patients. In a previous study, the seroprevalence rates of measles-specific IgG antibodies have been found to be 94.1%, 94.2%, and 96.6% in Rwandan patients, Swedish patients, and Swedish students, respectively (20). In previous studies, the seroprevalence rate of measles-specific IgG antibodies has been reported as 88%–95% (11, 21). In a study conducted in all healthcare workers, measles immunity has been detected as 88.1%. In a comprehensive report, measles immunity has been evaluated in age groups and found to be 72% in ages 18–25 years, 88.8% in ages 26–35 years, 95.2% in ages 36–45 years, and 91.8% in ages >45 years, respectively (22).

In a literature from Turkey, a total of 803 sera have been tested for anti-measles antibodies. Seropositivity rate has been reported as 90.4% for measles IgG (23). The percentage of susceptibility to measles has been found to be 0.24% (24). Our results appear to be lower than the literature. It can be related to vaccination history of the patients.

In our study, we found anti-mumps IgM and IgG as 2.5% and 87.5%, respectively. In a previous study, mumps seropositivity has been tested among measles seropositives, and the rate has been detected as 87.0% (18). In a study from Turkey, mumps seroprevalence has been reported as 90.4% (23). Our results are similar with the literature.

In our present study, we determined anti-toxoplasma IgM and IgG antibodies as 0% and 40%, respectively. The sensibility to toxoplasma was found to be 60%. In a previous study, anti-toxoplasma IgG has been found to be 29.9% among the participants, and anti-toxoplasma IgM has been detected as 0.37%. In another study, toxoplasma seroprevalence has been studied in pregnant women, and the seroprevalence in the first, second, and third trimesters has been reported as 30.4%, 30.6%, and 26.1%, respectively (25). In a meta-analysis, Malary et al. (26) investigated 43 studies with a total sample size of 22,644 for toxoplasma seroprevalence. The pooled seroprevalence of anti-toxoplasma IgG and IgM antibodies has been reported as 41.3% and 4.0%, respectively. In another meta-analysis, Mizani et al. (27) reported *Toxoplasma gondii* seroprevalence in Iranian women and found to be 43% in pregnant women and 33% in girls and the childbearing age groups. Our results are similar with Malary's and Mizani's meta-analysis.

In a literature from Turkey, anti-toxoplasma antibodies have been presented as 31.7% (9). In addition, in a previous study, 804 serum samples have been collected from pregnant women, and toxoplasma IgM and IgG seropositivity rates have been found to be 0.2% and 36.9%, respectively (15). In another study, toxoplasma serologies have been evaluated in pregnant women, and toxoplasma IgG seropositivity has been found to be 36.0% and toxoplasma IgM seropositivity has been found to be 0.3% (19). In a different study, anti-*T. gondii* IgG seropositivity and anti-*T. gondii* IgM seropositivity have been calculated as 41.1% and 4.3% in pregnant women, respectively (28). In addition, 3340 pregnant women were evaluated for toxoplasma IgM and IgG antibodies. IgM and IgG seropositivity rates have been found to be 3.6% and 57%, respectively (29). Our results are in the range of reported rates in Turkish studies.

In the present study, we found parvovirus B19 IgM seropositivity and seronegativity as 5% and 95%, respectively. In addition, parvovirus B19 IgG was found to be 95%. Dual positivity was not seen in the group. In a previous study, 6583 sera have been collected from adults, and 649 sera have been collected from healthy Thuringian children and adolescents. The overall parvovirus B19 seroprevalence has been found to be 72.1% in adults, 66.9% in adolescents (18–19 years), and 79.1% in the elderly. In another study, parvovirus seroprevalence has been detected as 75% in those aged >45 years (30). Similar rates have been reported in the European population when Belgian (74%), Italian (79%), and German (77%) blood donors were tested (31-33). In another study, a total of 1633 samples have been evaluated for parvovirus B19 IgM, and 540 samples have been detected for both parvovirus B19 IgM and IgG antibodies. Parvovirus B19 IgM antibodies have been found to be 7.53%, and seroprevalence of IgG antibodies has been found to be 27.96%. Dual positivity (IgG and IgM) has been found to be 2.40% (34).

In a study from Turkey, a total of 156 pregnant women have been analyzed for parvovirus B19. While parvovirus B19 IgG has been found to be 64.7%, parvovirus B19 IgM positivity alone has been detected in any women. Both parvovirus B19 IgG and IgM have been found to be 1.9% (35). In studies conducted in different patient and age groups, parvovirus seroprevalence has been reported as 16%–64% (36-41). When both international and national studies for parvovirus serology were compared, it appeared that parvovirus B19 seropositivity was detected to be higher in patients with tinnitus.

In conclusion, infections may be a cause for tinnitus. There are many rates about viral seroprevalence in the literature. However, to the best of our knowledge, this is the first study conducted in patients with tinnitus. When both international and national studies for parvovirus serology were compared in different patient groups, higher rates for parvovirus B19 seropositivity have been observed in patients with tinnitus in the present study. More comprehensive and more patients included in the study may contribute to the literature.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Fırat University Ethical Committee [2019/10 (03); Date 13.06.2019; Approval No: 10 (03)].

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Review

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Migraine and Fish Oil

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Considering the importance of migraine as the seventh cause of disability globally, this study was conducted to evaluate the effectiveness of fish oil and omega-3 polyunsaturated fatty acids (PUFA) on migraine. In this review article, we included all clinical trials and review articles from four databases (Pubmed, the Cochrane database of systematic reviews, Scopus, and Clinicalkey), published from January 1, 1990, to August 7, 2018, in which the treatment effects of fish oil or PUFA for the prevention or control of migraine attacks, either in basic science or clinical field, have been studied. At first, 54 articles or book chapters were found, and after reviewing their study design, 13 clinical trials and review articles were included in the study. Most of reviewed articles, including five clinical trials and four review articles, represented the positive impact of fish oil and omega-3 PUFA for improvement in frequency, intensity, or duration of migraine headache; however, a definite daily dosage and duration of treatment have not been defined. Although the evidence that supports the positive impact of fish oil and PUFA in the prevention and control of migraine is frequent, more evidence and longitudinal study designs are required to confirm the positive impact of fish oil on migraine. Furthermore, research is needed to define an appropriate daily dosage and treatment duration of fish oil and PUFA in migraine patients.

Keywords: Fish oil, migraine, omega-3 fatty acids

INTRODUCTION

Migraine manifests by recurrent, episodic headache attacks, which may or may not be preceded by a focal neurologic symptom (aura) (1-3). It is a debilitating disorder, affecting 2.6%–21.7% of general population, worldwide (4). Its lifetime prevalence has been reported to range between 13% and 33% (5). Self-reported prevalence rates of migraine and severe headache among US adult population were reported as 15.3% (9.7% for men and 20.7% for women) (6). Ninety percent of all headaches are either migraine, tension-type headache, or a mixture of them (7). The Global Burden of Disease Study 2015 represented migraine as the seventh cause of disability globally (8). A higher prevalence of this disorder has been reported in adults aged 18–44 years, the unemployed, people with lower family income, and the elderly and disabled individuals (6).

The mechanisms and contributing factors of a migraine attack are described in Figure 1 (2).

Migraine treatment includes both preventive therapy, for reducing the frequency and severity of migraine attacks, and acute therapy, for aborting acute symptoms. Treatment can be divided into pharmacological and psychological intervention approaches (9, 10), or specific and non-specific medications (11).

Fish and fish oils are rich in omega-3 polyunsaturated fatty acids (PUFA). They have several cellular and physiologic mechanisms of action, which produce the anti-inflammatory effects of this compound (12).

Some previous studies demonstrated that the fish oil and PUFA intake could be effective in the prevention or control of migraine due to their anti-inflammatory properties, vascular relaxation effects, and inhibition of serotonin release from platelets (7); and some other did not confirm a positive impact of fish oil on migraine. The aim of this research was to review published scientific manuscripts in which the effectiveness of fish oil in the prevention or acute treatment of migraine attacks has been assessed.

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We searched clinical trials and reviewed articles in four databases (Pubmed, the Cochrane database of systematic reviews, Scopus and Clinicalkey) from January 1, 1990, to August 7, 2018. At first, all of clinical trials, systematic reviews, and review articles that used the entry terms ("Disorder, Migraine" OR "Disorders, Migraine" OR "Migraine Disorder" OR "Migraine" OR "Migraines" OR "Migraine Headache" OR "Headache, Migraine" OR "Headaches, Migraine" OR "Migraine Headaches" OR "Acute Confusional Migraine" OR "Acute Confusional Migraines" OR "Migraine, Acute Confusional" OR "Migraines, Acute Confusional" OR "Status Migrainosus" OR "Hemicrania Migraine" OR "Hemicrania Migraines" OR "Migraine, Hemicrania" OR "Migraines, Hemicrania" OR "Migraine Variant" OR "Migraine Variants" OR "Variant, Migraine" OR "Variants, Migraine" OR "Sick Headache" OR "Headache, Sick" OR "Headaches, Sick" OR "Sick Headaches" OR "Cervical Migraine Syndrome" OR "Cervical Migraine Syndromes" OR "Migraine Syndrome, Cervical" OR "Migraine Syndromes, Cervical") AND ("fish oil" OR "Omega 3 Fatty Acids") in title, abstract, or keywords were included. We also reviewed reference lists of included studies to identify the articles related to search criteria. We searched published manuscripts in all languages. Two reviewers updated searches of the abstracts.

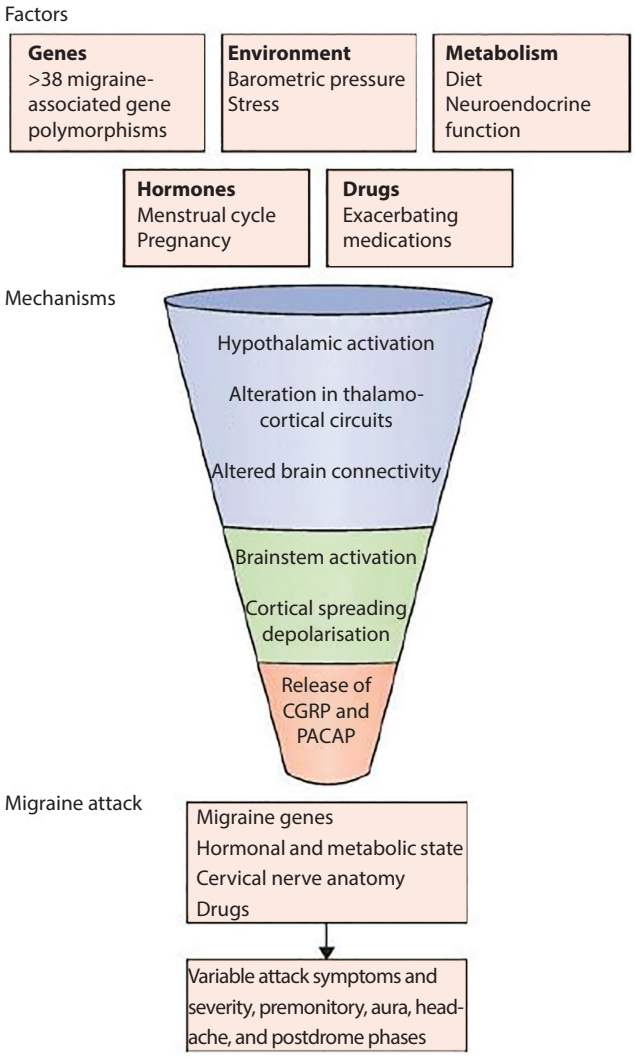

FIGURE I. Mechanisms and contributing factors of a migraine attack (Adapted from: Charles A. The pathophysiology of migraine: implications for clinical management. Lancet Neurol. 2018;17:174-82- Figure courtesy of Andrew Charles – used with permission)

We included clinical trials and review articles that studied the treatment effects of fish oil or PUFA in the prevention or control of migraine attacks, either in basic science or clinical field. Relevant articles were selected using a two-phase process. Two researchers reviewed all identified abstracts for eligibility. Second, full text articles were revised to determine the mentioned treatment effects of fish oil or PUFA, including the prevention or improvement in frequency, duration, and intensity or characteristics of migraine headache. All the interventional studies and review articles regardless of the duration and the size of study population were included. The evidence published before 1990 was excluded.

Two authors, not blinded to data sources, summarized the included studies. Overall quality assessment was performed emphasizing the treatment effects of fish oil or PUFA on the prevention of migraine attack or control of its symptoms.

CONCLUSION

We found 54 articles or book chapters in the four mentioned databases in which the association between fish oil and migraine has been studied. After reviewing the study design of these manuscripts, there were 13 clinical trials and review articles included in the study. The included studies are summarized in Table I. This table shows that six clinical trials and five review articles studied the treatment effect of fish oil or omega-3 PUFA on clinical aspects of migraine, such as its frequency, severity, or duration; two clinical trials studied the treatment effect of PUFA on immunologic aspects of migraine. Seven of the included studies were published from 2016 to 2018.

Most of reviewed articles including five clinical trials (13-16) and four review articles (14, 17-19) represented the positive impact of fish oil and PUFA on the improvement in frequency, intensity, or duration of migraine headache; however, a definite daily dosage and duration of treatment have not been defined.

There were three clinical trials (20-22) that reported no significant statistical difference between the case and control groups regarding the treatment effects of fish oil in the prevention or control of migraine. In addition, Rajapakse in his review article reported non-adequate evidence to confirm the prophylactic effect of PUFA for migraine (23), and Maghsoumi-Norouzabad showed that omega-3 PUFA did not have a positive effect in the frequency and intensity of migraine headache, although it was effective in the reduction of migraine duration (14).

Soares evaluated 60 patients with chronic migraine undergoing prophylactic treatment with amitriptyline. The patients who received omega-3 PUFA for 2 months were compared to the control group receiving placebo, and they experienced a reduction in the number of days of headache. Furthermore, it was suggested that omega-3 PUFA could be useful in the prevention of migraine headache (13). Ramsden (15) and Tajmirriahi (16) reported a similar positive effect of fish oil or PUFA in the prevention of headache attacks in their clinical trials conducted among the adult study population. Ramsden applied a combination of

TABLE I. Characteristics of included clinical trials and review articles describing the treatment effects of fish oil or omega-3 poly unsaturated fatty acids in the prevention or control of migraine (up to August 7, 2018)

			If the study is RCT			
The first author and publication year	**Country**	**Study design**	**Description of intervention and control (if applicable) groups**	**Duration of intervention (days)**	**Participants (study sample size)**	**Findings**
Soares A. (2018)	Brazil	Double- blinded, randomized, and placebo-controlled clinical trial	The case group: polyunsaturated omega-3 fatty acids the control group: placebo	60	Patients with chronic migraine (n=60)	In the case group, 66.7% of participants had a reduction >80.0% per month in the number of days with headache, while in the control group, the same improvement occurred in 33.3% of patients. The difference was significant.
Soveyd N. (2018)	Iran	Randomized clinical trial	Four groups: One group received omega-3 fatty acids, one group nano-curcumin, one group a combination of both, and the last group a placebo	60	Patients with episodic migraine (n=72)	A significant reduction in attack frequency was observed in the combination group.
Maghsoumi Norouzabad L. (2017)	Iran	Systematic review and meta-analysis of randomized controlled trials				Omega-3 intake had no effect on the frequency and severity of migraine, but it had a reduction effect on the duration of migraine attacks.
Abdolahi M. (2017)	Iran	Randomized clinical trial	Four groups: one group received omega-3 fatty acids, one group nano-curcumin, one group a combination of them, and the last group a placebo	60	Patients with episodic migraine (n=72)	A significant reduction in attack frequency was found in the combination group.
Fayyazi A. (2016)	Iran	Double-blinded randomized clinical trial	The case group: sodium valproate and 1 g of omega-3; the control group: sodium valproate and a placebo	60	Children aged 5–15 years with a diagnosis of migraine (n=25)	The average number of headache attacks per month and the severity of attacks decreased significantly in both groups; however, no significant difference was observed between the two groups.
Martin VT. (2016)	USA	Narrative review article				Low fat and high omega-3/ low omega-6 fatty diets decrease the frequency of migraine attacks.
Rajapakse T. (2016)	Canada	Review article				Inadequate evidence to support or refute the polyunsaturated fatty acids use in migraine prophylaxis.
Ramsden CE. (2013)	USA	Randomized, ingle-blinded, parallel group	The case group: high n-3 plus low n-6 diet the control group: low n-6 diet	84	Ambulatory adult patients with chronic daily headache (headaches ≥4 hours per day and ≥15 days per month for at least 3 Months, and a headache history of ≥2 years) (n=67)	The combination of high n-3 with concurrent reduction in n-6 fatty acids diet produced significant improvements in headache hours per day, severe headache days, and headache-related quality of life compared to baseline, and compared to the n-6-lowering diet.
Tajmirriahi M. (2012)	Iran	Single-blind randomized clinical trial	The case group: sodium valproate 400 mg daily plus fish oil supplementation the control group: 400 mg/day sodium Valproate	90	Adult patients with migraine headache (n=67)	A significant decrease in the duration, monthly frequency, and severity of headache was observed after Months 1, 2, and 3 in both groups There was a significant reduction in headache severity and frequency in the case group in comparison with the control group.
Simopoulos A. (2002)	USA	Review article				Dietary supplementation with fish oils is effective in several inflammatory and autoimmune diseases in humans, such as migraine headaches.
Harel Z. (2002)	USA	randomized, double-blind, cross-over study	2 months fish oil, 1 month washout period, and 2 months placebo (olive oil)	60	Adolescents with frequent migraines for at least 1 year (n=27)	A significant reduction in the headache frequency, duration, and severity during fish oil and also during placebo treatment was observed, with no significant difference between treatments.
Pradalier A. (2001)	France	16 weeks double-blind clinical trial with 4 weeks single-blinded placebo run-in period	The case group: omega-3 polyunsaturated fatty acid 6 gram per day the control group: placebo	112	Migraine patients (96 individuals taking omega-3 polyunsaturated fatty acid and 87 taking placebo)	The total number of migraine attacks was significantly lower in the case group. The mean intensity and duration of migraine were not significantly different between the two group Despite a run-in placebo period, a strong placebo effect was observed in this study.
McCarty M. (1996)	USA	Review article				Fish oil can be safe and effective in migraine prevention due to its platelet-stabilizing and antivasospastic actions.

omega-3 PUFA intervention besides the reduction of omega-6 fatty acids in a daily food program (15). Tajmirriahi compared the treatment effect of fish oil administration (180 milligram/day) plus sodium valproate 400 mg/day for 3 months in migraine patients with those who received only sodium valproate. In this research, a significant reduction in headache frequency was observed only during the Ist month of treatment; and this reduction was not significant during the 2nd and 3rd month of treatment (16). Soveyd (24) and Abdolahi (25) evaluated the effect of omega-3 PUFA on immunologic aspects of migraine in their clinical trials, and headache frequency was the secondary outcome that they examined. They observed a significant reduction in migraine attacks in patients who received a combination of omega-3 PUFA and nano-curcumin.

Fayyazi examined the treatment effect of omega-3 PUFA in pediatric migraine. He observed that children aged 5–15 years treated with a combination of omega-3 PUFA (1 gram per day) and sodium valproate for 2 months had a reduction in headache frequency and severity; however, the difference was not statistically significant between the case and control groups (22).

Although multiple factors and mechanisms have been described in the pathophysiology of migraine attacks (2), the origin of headache is not completely understood; recent evidence shows the effect of some vasomodulators, released by peripheral nerve endings on blood vessels in the scalp and meninges; furthermore, an inflammation and edema in blood vessels, with an increased sensitivity to mechanical stimulation are thought to be related to headache initiation. In addition, some receptors, such as nitric oxide, glutamate, and vanilloid, are also supposed to be involved in migraine (7). Some other evidence suggested that structural brain changes were more common in migraine patients, especially the patients with aura, than in control groups (26).

The exact mechanism of action of fish oil and omega-3 PUFAs in the prevention and control of migraine is still unclear, but it seems that their effect to inhibit multiple aspects of inflammation (27, 28); their effects on neuropeptides, neuro-receptors, and ion channels (29, 30); sympathetic nervous system (31); and also their vasomodulation impact (32) can justify their positive effect to improve migraine headache.

The most important limitation of this study was a non-specific quality assessment of included studies. It is suggested to future researchers to evaluate the treatment effect of fish oil and omega-3 PUFA with a different dosage and duration on the frequency, severity, and duration of migraine attacks.

Although the evidence supporting the positive impact of fish oil and PUFA in the prevention and control of migraine is more frequent, more evidence and longitudinal study designs need to confirm the positive impact of fish oil on migraine. Furthermore, research is needed to define an appropriate daily dosage and treatment duration of fish oil and PUFA in migraine patients.

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