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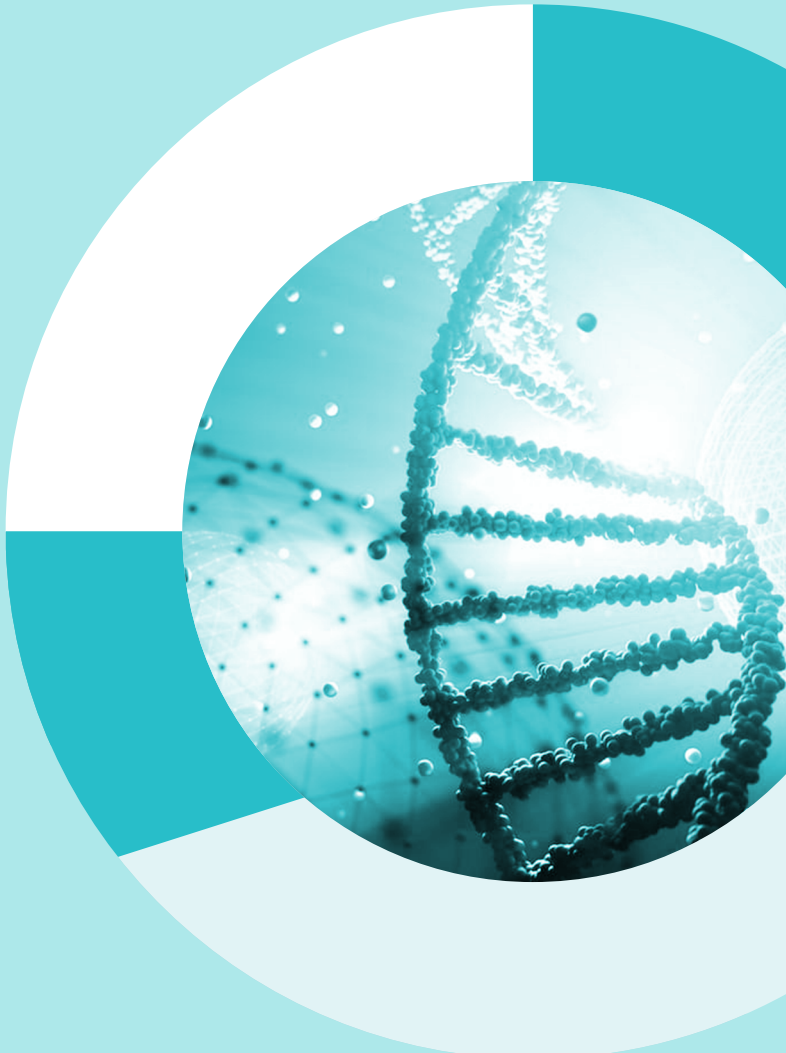

Official Journal of Cyprus Turkish Medical Association

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This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles. As of 2022, the journal has become a bimonthly publication, publishing in February, April, June, and August, October and December. The journal's publication language is English. (E-ISSN:2536-507X)

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Cyprus Journal of Medical Sciences adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

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- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

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- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
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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

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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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Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
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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
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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/ncidodIElD/cid.htm.

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RESEARCH ARTICLE

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Care Dependency of Individuals Discharged from Hospital and Its Effect on Their Readiness for Discharge

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Abstract

BACKGROUND/AIMS: This study was carried out to examine the readiness to discharge, and the care dependency of patients who had been hospitalized for at least two days in surgical and internal clinics who were then recommended for discharge.

MATERIALS AND METHODS: In this descriptive study, a simple random sampling method in a training and research hospital was used between April 10th, 2018 and April 10th, 2019. Five hundred forty patients who agreed to participate in this study were included. The Patient Information Form covering the sociodemographic characteristics of the patients, the Care Dependency scale, and the Readiness for Discharge scale (RDS) were used to collect the research data.

RESULTS: The median age of the patients was 61.00 years and the median of hospital stay was 5 days. It was determined that the median score of care dependency of those patients who were recommended for discharge was moderately independent with a medium score on meeting their care needs of 46.00. When the median score of the RDS was examined, it was determined that, for those people who were not ready for discharge, it was high with a total scale score of 6.18.

CONCLUSION: The use of scales for care needs and discharge may prevent the early discharge of patients from hospital, and thus, may help to reduce the development of complications after discharge, re-hospitalization and additional medical expenses. In line with the results of this study, it is clear that patients need pre-discharge education.

Keywords: Discharge, readiness, care dependency, patient

INTRODUCTION

Health problems, hospitalization and the treatment process cause an individual to have stress, anxiety and feelings of uncertainty about their future. The hospital process negatively affects the physical functions of the individual and leads to an increase in dependency and thus a decrease in their quality of life.[1] Dependency has physical, mental, emotional, cognitive, social, economic and environmental aspects, and care dependency is defined as the patient's need for professional support and request for a certain level of care depending on the decrease in their level of meeting their self-care needs and their dependency status.[2] In other words, care dependency is the restriction in life due to a disease or disability. This may be temporary, long-term or permanent.[3] Individuals who are discharged from hospital may have many difficulties, such as the continuation of their treatment at home, adaptation to their disease and/or the drugs they use.[1] Conditions of unpreparedness are caused by the inability of patients to manage their own needs and care needs after returning home, such as in carrying out daily tasks, caring for themselves, or their ability to perform their health care.[4]

Discharge planning is a dynamic, comprehensive and collaborative process which aims to encourage an individual to continue his/her care

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after discharge and to ensure that the caregiver can also provide the necessary service and support.[5] A well-planned discharge education ensures a decrease in the duration of hospital stay and an increase in the quality of care both in hospital and at home, resulting in improved patient satisfaction.[6] The use of a clinical assessment tool to evaluate patient readiness for discharge has been recommended as an addition to standard care for discharge preparation.[7]

In the literature, it is emphasized that readiness to discharge is effective on developments of the necessary health behavior, on improvements in quality of life, on preventing recurrent hospitalizations and also on mortality.[8-10] Considering that training and counseling are important in preparing individuals for discharge, it is important to correctly determine the situation before discharge. In line with this, this study was carried out to examine the readiness to discharge and the care dependency of patients who had been hospitalized for at least two days in surgical and internal clinics and who then were recommended for discharge.

Research Questions

This study addressed the following specific research questions:

1. What are the levels of patients' readiness for discharge from hospital?

2. What are the levels of care addiction of the patients when they are discharged from hospital?

3. What is the relationship between care addiction and readiness for discharge when patients are discharged from hospital?

MATERIALS AND METHODS

This study was a cross sectional study, carried out in an education and research hospital with a capacity of 430 beds, in a metropolitan center. This study was carried out with voluntary participants who were 18 years old or above, were literate, spoke Turkish, had no mental disorders, had been hospitalized in the internal medicine and surgical clinics of a training and research hospital between April 10th, 2018-April 10th, 2019 and were determined to be ready for discharge on their last day of hospitalization. Patients numbering at least ten times the total number of items (25 items) on the scales used in this study were targeted. While all those patients who met the inclusion criteria constituted the population of this study, the final sample consisted of 540 patients who agreed to participate using a simple random sampling method. The Patient Information Form including the sociodemographic characteristics of the patients, the Care Dependency Scale (CDS), and the Readiness for Discharge Scale (RDS) were used to collect the research data. The data were collected by the researchers at the end of the discharge day on the scheduled dates. Before the data were collected, the patients were informed about the objectives and scope of this study and asked whether they would volunteer to participate. Written and verbal consent of the participants was obtained. The forms were filled in during a 10-15-minute interview time and then collected by the researchers.

Patient Information Form

This form, which was prepared by the researchers, covered sociodemographic data such as the age and gender of the participants, and questions about their health status and requirements such as chronic disease, continuous drug use, and the need for care support.

Care Dependency Scale

The CDS is a scale which was developed by Dijkstra in Holland in 1998, based on the human needs of Virginia Henderson in order to evaluate patients' care dependency. The validity and reliability study of the CDS in Türkiye was performed by Yont et al.[11] The CDS is a scale consisting of 17 items covering the activities of daily living which determines the dependency levels of individuals and it is rated in a 5-point Likert-type format. The minimum and maximum scores which can be obtained from the scale are 17 and 85, respectively. A high score obtained from the scale indicates that the patient is independent in meeting their care needs.[11] Yont et al.[11] found the Cronbach's alpha value to be 0.91 in their validity study. In this study, it was found to have a reliability coefficient of 0.76.

Readiness for Discharge Scale

This scale was developed by Weiss et al.[12] All eight items of the RDS are evaluated between 0-10 points, and higher scores indicate a higher readiness. The validity and reliability study of the RDS in Türkiye was performed by Kaya et al.[13] The four sub-dimensions of the scale are *Personal Condition*, *Knowledge*, *Coping Skills* and *Expected Support*. Its Cronbach's alpha value was found to be 0.74 in their validity study, and it was found to have a reliability coefficient of 0.89 in this study.

Ethical Approval

This study was initiated after receiving approval from the hospital administration and the ethics committee (Sakarya University Faculty of Medicine Non-interventional Scientific Research Ethics Committee, approval number: 71522473/050.01.04/70). Informed written consent was obtained from the participants on a voluntary basis.

Statistical Analysis

Data were evaluated with the statistical software program IBM SPSS Statistics 21. It was observed that numerical variables did not conform to normal distribution while evaluating the data of this study. Frequency distributions were given for categorical variables. Whether there was a difference between two independent groups was analyzed by the Mann-Whitney U test, and the Kruskal-Wallis test was used to determine whether there was a difference among more than two independent groups. Cronbach's alpha values were interpreted for the reliabilities of the scales. The Cronbach's alpha value, which is an internal consistency measure, was calculated in order to evaluate the reliabilities of the scales. The values in Table 1 are higher than 0.70, which is generally accepted as indicating sufficient reliability. The relationship between numerical variables was examined by the Spearman correlation test. The statistical analysis of this study was performed by the researchers.

RESULTS

The median age of 540 patients included in this study was 61.00 years and the median value of hospital stay was 5 days. 48.9% of the patients were female, 74.1% were married, and 69.4% were literate or primary school graduates. It was observed that most of the patients stated that they were unemployed (80.9%), had income equal to their expenses (80.7%), lived with their spouses (52.8%), received treatment in a surgical clinic (51.7%), did not smoke (63.0%) and had a regular dietary habit (68.9%), however, most of them (35.2%) were in the overweight group (25-29.9 kg/m^2). It was observed that the median score of care dependency of the patients who were determined to be ready for

discharge was moderately independent with the medium score on their meeting their care needs of 46.00. When the median score of the RDS was examined, it was determined that the number of people who were not ready for discharge was high with a total scale score of 6.18. In terms of the sub-dimensions of the RDS, *Personal Condition* had an average of 6.00, *Knowledge* had an average of 5.00, *Coping Skills* had an average of 6.00 and *Expected Support* had an average of 9.00 (Table 1).

When some characteristics of the patients and their readiness for discharge were examined, it was observed that there was a highly significant difference between the need for support for care and the total scale and its sub-dimensions ($p<0.01$). Similarly, there was a highly significant difference between *nutritional status and knowledge* and the total scale score ($p<0.01$), and there was a significant difference between *Personal Condition*, *Coping* and *Expected Support* ($p<0.05$) (Table 2).

In Table 2, 3, some characteristics of the discharged patients, and the relationships and significance between CDS and RDS are presented. Among the patients included in this study, it was observed that those who needed support for care were not ready for discharge, while those who did not need support for care were ready for discharge, and that the score difference between them was significant ($p<0.001$). Similarly, it was observed that those with regular dietary habits were ready for discharge and this made a significant difference compared to those who were not ready ($p<0.05$) (Table 2). The correlation coefficients between the characteristics of the patients ranged from 0.151 to 0.807, and the highest correlation was between the RDS *Personal Condition* and the RDS scores ($r=0.807$, $p<0.001$). There was a positive correlation between CDS and the RDS's sub-dimension of *Personal Condition* and a weak negative correlation with *Coping Skills* ($r=0.151$, $r=-0.183$, $p<0.001$) (Table 3).

DISCUSSION

The determination of hospitalized patients' levels of care dependency while preparing for their discharge from the hospital will improve the quality of nursing care and ensure the readiness of the patients to go home.

In this study, patients independently performed their care needs at the moderate level according to CDS, and according to RDS, it was determined that they were not fully ready for discharge. They mostly felt ready for discharge in the sub-dimensions of *Support*, *Personal Condition* and *Coping Skills* while they felt least ready for discharge in the sub-dimension of *Knowledge* according to their answers given on the RDS. The fact that the minimum score was obtained from the sub-dimension of *Knowledge* indicates that the patients needed discharge education (Table 1). In their study with patients over 60 years of age (n=200), Doroszkiewicz et al.[14] found that CDS was moderately independent.

Table 1. Mean CDS and RDS score of patients

Scale averages	n	Minimum	Maximum	Median
Care Dependency Scale	540	17.00	85.00	46.00
Readiness for discharge total	540	0.00	10.00	6.18
RfD personal condition	540	0.00	10.00	6.00
RfD knowledge	540	0.00	10.00	5.00
RfD coping skills	540	0.00	10.00	6.00
RfD expected support	540	0.00	10.00	9.00

CDS: Care Dependency Scale, RDS: Readiness for Discharge Scale.

Table 2. Comparison of characteristics of patients with RDS

Variables		RfD personal condition	RfD knowledge	RfD coping skills	RfD expected support	RfD total
Needing support for care	Yes (n=246)	4.25	3.00	4.00	8.00	4.62
	No (n=294)	7.00	6.00	7.00	10.00	7.12
	Test statistics	5060,500; **0.000****	48944,500; **0.000****	54171,500; **0.000****	45250,500; **0.000****	55140,500; **0.000****
Chronic disease	Yes (n=311)	6.00	5.00	6.00	9.00	6.12
	No (n=229)	6.00	5.00	6.00	10.00	6.25
	Test statistics	35820,500; 0.906	32976,500; 0.140	37761,500; 0.229	39124,500; 0.138	36212,000; 0.737
Regular medication use	Yes (n=335)	6.00	5.00	6.00	9.00	6.25
	No (n=205)	6.00	4.50	6.00	9.50	6.12
	Test statistics	31161,000; 0.920	31819,500; 0.151	31926,000; 0.169	32532,500; 0.278	33791,500; 0.756
Regular dietary habit	Yes (n=372)	6.50	5.50	6.50	9.00	6.75
	No (n=168)	5.25	3.25	5.50	8.50	5.00
	Test statistics	26242,500; **0.003***	24076,000; **0.000****	27005,000; **0.011***	26131,000; **0.001***	23133,000; **0.000****

Mann-Whitney U test, *p<0.05; **p<0.01.

Table 3. Correlations between the dimensions of CDS, RDS

	1	2	3	4	5	6
1. Care Dependency Scale	1					
2. Readiness for Discharge Scale	0.076	1				
3. RfD personal condition	**0.151****	**0.807****	1			
4. RfD knowledge	-0.083	**0.733****	**0.567****	1		
5. RfD coping skills	**-0.189****	**-0.798****	**-0.616****	**-0.423****	1	
6. RfD expected support	-0.007	**0.686****	**0.301****	**0.256****	**0.421****	1

Spearman correlation test *p<0.05; **p<0.01. CDS: Care Dependency Scale, RDS: Readiness for Discharge Scale.

In another study, they found that patients staying in internal medicine and surgical clinics had higher levels of dependency according to their CDS scores.[15] In their study, Kaya et al.[13] determined that their patients (n=1,579) were not fully ready according to their RDS scores. In their study carried out on patients who had had a heart attack and were preparing for discharge, Kosobucka et al.[16] found that the patients were moderately ready to be discharged according to their scores obtained and that there was a significant relationship between their economic conditions and the mean score of the scale for readiness. In another study, it was emphasized that 95.36% of the patients felt ready for discharge and the reason for this high ratio was due to the social support received.[17] In their study carried out to determine the information needs of patients at discharge, Yalcin et al.[18] determined that patients needed information especially about their drugs. Guclu and Kursun[6], determined that patients needed information about care at home. It is known that nurses preparing discharge plans cannot play an active role in the preparation process due to insufficient staff numbers and work load density, and they also face problems such as the inappropriateness of the patient and their family for the preparation process.[9,19] To improve health team communication and collaboration regarding hospital discharge; improve the patient experience of discharge measured by patient-reported quality of discharge teaching, readiness for discharge, and post-discharge coping difficulty; and reduce readmissions and emergency department visits post-discharge.[20] In these studies, it was generally observed that individuals were not fully ready for discharge, which suggested that the education of the patients and the caregivers in the clinic was insufficient and that there was not enough planning regarding discharge education. The care support needed by the patients while preparing for discharge should be determined and met before discharge.

According to the results of this study, it was determined that those who stated that they needed support for care were not ready for discharge and that those with regular dietary habits were ready for discharge (Table 2). Kaya et al.[21], who applied the RDS in their study, stated that the presence of someone who could help in care at home or who lived together with the patient made it easier to be ready for discharge. Orak and Sezgin[22], indicated that the caregivers' education level affected the care burden, and that the duration of providing care to the patient and the care burden scores of those who were literate were higher, while Mollaoglu et al.[23] stated that those who provided support for care were first-degree relatives (husbands, children, parents, siblings) and that almost half of the caregivers met all the needs of the patient by themselves. Ozturk and Karatas[24], stated that receiving a balanced diet and the consumption of preferred meals which met their nutritional needs caused patients to have positive feelings. It is known that irregular and poor nutrition at home after discharge leads to a lack of energy, fatigue, an inability to perform daily activities and psychological disorders in the patient.[25] In their study, regular dietary habits accelerated the patient's readiness for discharge in terms of coping with their disease and meeting their daily needs, and the fact that the care support needed is not provided to the individual can lead to a failure to maintain home-care after discharge.

There was a positive correlation between CDS and the RDS sub-dimension of *Personal Condition* and a weak negative correlation with *Coping Skills* (Table 3). The factors affecting patients' readiness for discharge in the sub-dimension of *Coping Skills* consisted of age, gender, marital status, educational level, and the presence of a person living with the patient. In the sub-dimensions of *Personal Condition* and *Coping Skills*, it was indicated that the patients discharged before being ready had a higher ratio of having one of the following results; unplanned re-hospitalization, mortality or other negative consequences.[21] With respect to *Personal Condition*, males are thought to have more difficulty in meeting their care needs. In their study carried out with male patients older than 70 years, Provencher et al.[26] determined that receiving support at home (spouse, child) after discharge positively affected patients' readiness for discharge. In a study carried out in Indonesia, there was found to be a positive relationship between coping skills and discharge education.[27] Determining priority needs and accordingly planning care and discharge by considering the personal situation of the patients will ensure that the process at home continues healthily. Furthermore, male patients in society are in need of extra care. The fact that a primary caregivers (spouse, child, parent, sibling) shares the same house with the patient and has sufficient knowledge and competence regarding their care will increase the comfort of the patient. Therefore, it is necessary to include the people who are primarily responsible for giving care in the discharge education.

Study Limitations

This research was conducted in a single center. Therefore, it was limited to those patients who met the sampling criteria and agreed to participate. Therefore, these research results cannot be generalized to the entire population.

CONCLUSION

In our study, we found that the care dependency score of the patients was moderate and the number of people who were not ready for discharge was high. The use of scales for care needs and discharge may prevent the early discharge of patients from hospital, thus, they may help to reduce the development of complications after discharge, re-hospitalization and/or additional medical expenses. When patients are discharged, their self-care skills should be fulfilled either by themselves or by a caregiver. Discharge education and care practices should be provided by healthcare professionals and there should be a sufficient

number of health workers to ensure this. Furthermore, it is necessary to know the characteristics of caregivers in order to determine the groups at risk of having difficulties, to create support groups according to specified characteristics, to determine resources in the planning of the services to be provided, to improve the services provided by health institutions and to create health policies.

MAIN POINTS

- The use of scales for care needs and discharge can prevent the early discharge of patients from hospital.
- They can contribute to an improvement in the services provided by health institutions and the formulation of health policies.
- After discharge, they can help to reduce complications, re-hospitalization, and/or medical costs.

ETHICS

Ethics Committee Approval: This study was initiated after receiving approval from the hospital administration and the ethics committee (Sakarya University Faculty of Medicine Non-interventional Scientific Research Ethics Committee, approval number: 71522473/050.01.04/70).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.T., Ö.D., Design: Ö.T., Ö.D., Supervision: Ö.D., Materials: Ö.T., Ö.D., Data Collection and/or Processing: Ö.T., Ö.D., Analysis and/or Interpretation: Ö.T., Ö.D., Literature Search: Ö.T., Ö.D., Writing: Ö.T., Ö.D., Critical Review: Ö.T., Ö.D.

DISCLOSURES

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

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REFERENCES

1. Hestevik CH, Molin M, Debesay J, Bergland A, Bye A. Older persons' experiences of adapting to daily life at home after hospital discharge: a qualitative metasummary. BMC Health Serv Res. 2019; 19(1): 224.
2. Korhan EA, Yont G, Tokem Y, Karadag O, Sarıoglu E, Yıldız K. Determination of Care Dependency Level of Patients Staying in Medical and Surgical Clinics. Journal of Anatolia Nursing and Health Sciences. 2013; 16(4): 199-204.
3. Lohrmann C, Dijkstra A, Dassen T. Care dependency: testing the German version of the Care Dependency Scale in nursing homes and on geriatric wards. Scand J Caring Sci. 2003; 17(1): 51-6.
4. Rahmahwati IN, Riri M. Implementation of Nursing Round and Discharge Teaching to Improve Discharge Readiness for Patients Post Hip Surgery: A Literature Review. IJNHS. 2019; 2(1): 40-7.
5. Toufighi H, Sharifi V, Rad JA, Shadloo B. Development and Implementation of Discharge Planning Service in Roozbeh Hospital. IJPCP 2018; 24(1): 56-69.
6. Guclu A, Kursun S. Learning Needs at Discharge of Patients Hosiptalized in the General Surgery Clinic. Journal of Anatolia Nursing and Health Sciences. 2017; 20(2): 107-13.
7. Weiss ME, Yakusheva O, Bobay KL, Costa L, Hughes RG, Nuccio S, et al. Effect of Implementing Discharge Readiness Assessment in Adult Medical-Surgical Units on 30-Day Return to Hospital: The READI Randomized Clinical Trial. JAMA Netw Open. 2019; 2(1): e187387.
8. Howard-Anderson J, Busuttil A, Lonowski S, Vangala S, Afsar-Manesh N. From discharge to readmission: Understanding the process from the patient perspective. J Hosp Med. 2016; 11(6): 407-12.
9. Weiss ME, Sawin KJ, Gralton K, Johnson N, Klingbeil C, Lerret S, et al. Discharge Teaching, Readiness for Discharge, and Post-discharge Outcomes in Parents of Hospitalized Children. J Pediatr Nurs. 2017; 34: 58-64.
10. Dogu OZ, Kaya H. Compliance of the Web-based Distance Training and Consultancy on Individual's Treatment having Suffered Myocardial Infarction and its Effects on Well-being. J Coll Physicians Surg Pak. 2018; 28(12): 953-9.
11. Yont G, Korhan EA, Khorshid L, Eser I, Dijkstra A. Investigation of Validity and Reliability of Career Dependency Scale (Bakım Bağımlılığı Ölçeğinin) in Elderly Individuals. Turkish Journal of Geriatrics. 2010; 13(Suppl): 12.
12. Weiss ME, Costa LL, Yakusheva O, Bobay KL. Validation of patient and nurse short forms of the readiness for hospital discharge scale and their relationship to return to the hospital. Health Serv Res. 2014; 49(1): 304-17.
13. Kaya S, Sain Guven G, Teleş M, Korku C, Aydan S, Kar A, et al. Validity and reliability of the Turkish version of the readiness for hospital discharge scale/short form. J Nurs Manag. 2018; 26(3): 295-301.
14. Doroszkiewicz H, Sierakowska M, Muszalik M. Utility of the Care Dependency Scale in predicting care needs and health risks of elderly patients admitted to a geriatric unit: a cross-sectional study of 200 consecutive patients. Clin Interv Aging. 2018; 13: 887-94.
15. Kılıç H, Cevheroğlu S, Görgülü S. Determination of Care Dependency Level of Patients Staying in Medical and Surgical Clinics. DEUHFED. 2017; 10(1): 22-8.
16. Kosobucka A, Kasprzak M, Michalski P, Pietrzykowski L, Fabiszak T, Felsmann M, et al. Relation of the Readiness for Hospital Discharge after Myocardial Infarction Scale to socio-demographic and clinical factors. An observational study. Med Res J. 2018; 3(1): 32-7.
17. Qiu C, Feng X, Zeng J, Luo H, Lai Z. Discharge teaching, readiness for discharge, and post-discharge outcomes in cataract patients treated with day surgery: A cross-sectional study. Indian J Ophthalmol. 2019; 67(5): 612-7.
18. Yalcin S, Arpa Y, Cengiz A, Dogan S. A Comparison of Nurses' and Patients' Opinions About Discharge Education Needs. JERN. 2015;12(3): 204-9.
19. Yildirim M, Bayraktar N. The Roles of Nurses Working in Surgical Clinics in Discharge Planning Process and the Factors Affecting Their Roles. Turkiye Klinikleri J Nurs Sci. 2010; 2(2): 73-81.
20. Opper K, Beiler J, Yakusheva O, Weiss M. Effects of Implementing a Health Team Communication Redesign on Hospital Readmissions Within 30 Days. Worldviews Evid Based Nurs. 2019; 16(2): 121-30.
21. Kaya S, Guven GS, Teles M, Aydan S, Korku C, Kar A. Dimensions of Readiness for Discharge: Determinants and Associations with Patient Outcomes and Hospital Expenditures. Hacettepe Journal of Health Administration. 2018; 21(2): 305-34.
22. Orak OS, Sezgin S. Caregiver Burden in Family Members of Cancer Patients. Journal of Psychiatric Nursing. 2015; 6(1): 33-9.
23. Mollaoglu M, Tuncay F, Fertelli T. Care Burden of Care Givers of Stroke Patients and Related Factors. DEUHYOED. 2011; 4(3): 125-30.
24. Ozturk C, Karatas H. Orem's Self-Care Deficit Theory of Nursing and Nursing Care in Posttraumatic Epilepsy. Journal of Atatürk University School of Nursing. 2008; 11(2): 85-91.
25. Westergren A. Nutrition and its relation to mealtime preparation, eating, fatigue and mood among stroke survivors after discharge from hospital - a pilot study. Open Nurs J. 2008; 2: 15-20.

26. Provencher V, D'Amours M, Viscogliosi C, Guay M, Giroux D, Dubé V, et al. Risks Perceived by Frail Male Patients, Family Caregivers and Clinicians in Hospital: Do they Change after Discharge? A Multiple Case Study. Int J Integr Care. 2019; 19(1): 4.

27. Nurhayati N, Songwathana P, Vachprasit R. Surgical patients' experiences of readiness for hospital discharge and perceived quality of discharge teaching in acute care hospitals. J Clin Nurs. 2019; 28(9-10): 1728-36.

RESEARCH ARTICLE

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Quality of Life in the Third Trimester of Pregnancy in Patients with Gastroesophageal Reflux Disease

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Abstract

BACKGROUND/AIMS: Health-related quality of life (QoL) relating to mental, physical and social functioning in pregnant women with gastroesophageal reflux disease (GERD) may depend on several factors. The aim of this study was to investigate the impact of GERD on the QoL in the advanced stages of pregnancy.

MATERIALS AND METHODS: A total of 53 pregnant women suffering from GERD (group 1) and 54 age, body mass index (BMI) and gestational age-matched pregnant controls (group 2) were enrolled. The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was completed to measure of health-related QoL, and the Gastroesophageal Reflux Disease Questionnaire was used to assess the classical symptoms of reflux disease. Socio-demographic variables including age, gravidity, parity, BMI and previous history of GERD were noted.

RESULTS: SF-36 scores were found to be significantly lower in the pregnant women with GERD in regard to the following domains: their general health ($p<0.01$), mental health ($p<0.01$), and their mental component score ($p=0.01$). Educational status and GERD symptoms before pregnancy were not found to have an impact on QoL in pregnant women with GERD.

CONCLUSION: Pregnant women with GERD seem to have a poorer QoL in many respects.

Keywords: Pregnancy, quality of life, gastroesophageal reflux disease

INTRODUCTION

Most pregnant women experience symptoms of gastroesophageal reflux disease (GERD) at some point during their pregnancy. According to the Montreal consensus, GERD can be defined as troublesome symptoms and/or complications due to reflux of the stomach contents to the esophagus.[1] The most common reasons for GERD development in pregnancy are alterations in the gastrointestinal transit time due to hormonal changes, decreased lower esophageal sphincter pressure and increased intra-abdominal pressure due to the expanding gravid uterus.[2,3] GERD in pregnancy is often new onset but some women may have had symptoms before pregnancy. The most common symptoms of GERD which are seen in pregnancy are heartburn and acid reflux, which are traditionally considered innocuous.[4] Although heartburn can happen at any time during pregnancy, the last three months deserves special attention because it presents a special challenge for the clinician.[5] Moreover, heartburn and acid reflux, which are clinical signs of GERD, significantly affects the quality of life (QoL) in pregnant women, especially in their third trimester.

The impact of GERD on QoL in certain disease conditions has been demonstrated in multiple clinical studies, but there has been little or scarce data which analyzed QoL in third trimester pregnant women with GERD.[3] Analyzing QoL in pregnant women is of great importance because it is an important indicator of the strength of health and

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wellness. In this context, several generic instruments including the Nottingham Health Profile, the Psychological General Well-Being Index, the Quality of Well-Being Scale and the 36-Item Short-Form Health Survey (SF-36) have been put forward to quantify QoL in distinct disease states, particularly in gastrointestinal system disorders.[6-8] Among these questionnaires, the SF-36 is the most widely used worldwide and it is designed to offer a concurrent measurement of both the individual's physical and mental health (MH) status. It has been particularly well-studied across a wide range of populations with specific conditions and it is considered to be an appropriate tool for describing health and QoL during pregnancy.[3]

The general belief is that health-related functional status during pregnancy changes only for the physical measures of health, and the impact of GERD on health-related QoL has not been sufficiently studied to date. The objective of this study was to investigate QoL in third trimester pregnant women with GERD. The primary hypothesis was that pregnant women in the advanced stages of pregnancy with GERD have a worse QoL than those without any of the signs or symptoms associated with GERD.

MATERIALS AND METHODS

Characteristics of the Patients

This study was a case-control study and it was conducted in accordance with the guidelines proposed by the World Medical Association of Helsinki. Ethical clearance was obtained from Çanakkale Onsekiz Mart University Faculty of Medicine Ethics Board (approval number: 2016-03, date: 17.02.2016). Written informed consent was obtained from all of the participating women.

The patients and controls included in this study were recruited from the outpatient clinic of the Department of Obstetrics and Gynecology, Çanakkale Onsekiz Mart University during a 6-month period. The study group consisted of 53 pregnant women with GERD followed up in the obstetrics and gynecology clinic of the same hospital. The control group consisted of 54 healthy pregnant women without symptoms of GERD who were admitted to the outpatient clinic for regular antenatal care.

The inclusion criteria were determined as a viable pregnancy of more than 28 weeks gestation, a lack of any systemic maternal diseases including, renal, pulmonary, gastrointestinal, or cardiovascular system disorders, an absence of any previously known psychiatric disorders, an absence of multiple pregnancies or any known obstetric complications. Pregnant women who had hormonal diseases, including diabetes mellitus or thyroid related disorders, were excluded from this study. Pregnant women who were using medications (including antidepressants, anti-psychotic or other psychiatric drugs), those who had current or past illicit drug abuse, those with past patterns of alcohol consumption, or those with cognitive impairments which could make it hard to complete the SF-36 were excluded.

Instruments

Gastroesophageal Reflux Disease Questionnaire

The Gastroesophageal Reflux Disease Questionnaire (GERDQ) (Table 1) is a unique, self-administered, patient-centered validated tool which was designed for healthcare professionals to improve and standardize symptom-based diagnosis and evaluations of treatment response in patients with GERD. It is a Likert-type (0-3) questionnaire which contains 6 questions with symptoms frequency scores to be completed by the patient. It comprises four positive predictors of GERD (heartburn and regurgitation, sleep disturbance because of these two reflux symptoms, and the need for over-the-counter medication) and two negative predictors of GERD (epigastric pain and nausea).[9] An overall GERDQ score of 0-18, and an impact score of 0-6 are used to compile a total score, which informs the clinicians' diagnosis of disruptive or inconveniencing GERD and allows for recommendations to be made to the patient. The GERDQ can be used to diagnose GERD with a diagnostic accuracy similar to that of a gastroenterologist at a cut-off value of 8 (out of 18) points with a specificity of 71.4% and a sensitivity of 64.6%.[10] A total GERDQ score of 8-10 indicates a 79% likelihood of GERD and 11-18 indicates an 89% likelihood of GERD.[11] The validation process for the GERDQ questionnaire in the Turkish general population was carried out by Mungan in 2012.[12]

Assessment of Quality of Life

In order to evaluate the QoL of women in their third-trimester, the SF-36 form was used. The SF-36 is a generic instrument developed by Ware and Sherbourne[13] which evaluates QoL for the last four weeks via eight dimensions of physical and MH including *physical functioning*, *role-physical*, *bodily pain*, *general health* (GH), *vitality*, *social functioning*, *role-emotional*, and MH. These 8 subscales are constructed from 36 items. Two additional measures, which are known as the Physical Health Component Score (PCS) and the Mental Health Component Score (MCS), can be derived as a summary. A high score achieved with this questionnaire indicates better physical and MH which are both related to QoL. The validation studies of the Turkish version of SF-36 were carried out on 100 patients with rheumatic disease by Koçyiğit et al.[14] in 1999.

Table 1. The Gastroesophageal Reflux Disease Questionnaire

	Question	Frequency score for symptom			
		0 day	1 day	2-3 days	4-7 days
1	How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2	How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3	How often did you have a pain in the center of the upper stomach?	3	2	1	0
4	How often did you have nausea?	3	2	1	0
5	How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6	How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take?	0	1	2	3

Statistical Analysis

The Statistical Package for Social Sciences version 19 (SPSS Inc., Chicago, IL, USA) for Windows was used to analyze the data. Continuous variables were tested for normality with the Kolmogorov-Smirnov test and are presented as mean ± standard deviation (SD). Student's t-test was used to compare continuous variables. Data found to be non-normally distributed were compared using the Mann-Whitney U test. A p-value <0.005 was used to indicate statistical significance.

RESULTS

A total of 53 pregnant women with GERD (mean age: 28.0±5.4 years) and 54 pregnant women without GERD (mean age: 27.7±5.4 years) as controls were enrolled in the present study. There were no statistically differences between the ages of the study participants. The mean pre-gestational body mass index of the two groups were similar (p=0.139). The level of education did not differ between the groups (p>0.005 in all subgroups). Twenty out of the 53 pregnant women with GERD reported a history of pregestational heartburn and/or regurgitation when not pregnant. The socio-demographic data of the two groups are summarized in Table 2.

The mean SF-36 scores for each variable including their physical and mental component summaries are shown in Table 3. In general, pregnant women with GERD had lower scores on both their physical and mental dimensions and this was statistically significant for GH (p<0.01), MH (p<0.01), and MCS (p=0.01). The differences for the other SF-36 domains were not statistically significant. The pregnant controls had higher SF-36 mean scores for GH (72.7) and MH (72.0) with over 70 points (Figure 1).

The pregnant women with GERD were divided into three groups according to their educational status. The education levels of the study participants were classified as low (illiterate or primary education up to 8 years), medium (high school, 8-12 years of education) and high (university level, more than 12 years of education). According to their educational status, the SF-36 scores did not differ between the pregnant women (p>0.05) (Table 4). Twenty out of the 53 patients were reported to experience GERD symptoms before pregnancy. Experiencing GERD before pregnancy did not affect their SF-36 scores compared with those pregnant women who did not experience any GERD symptoms before pregnancy (p>0.05) (Figure 2).

According to the GERDQ scores, the pregnant women with GERD were divided into 2 groups (GERDQ scores 8-10 and GERDQ scores 11-18). The SF-36 scores were reexamined between these subgroups of GERD. No significant difference was found in all eight domains of the SF-36 between these 2 GERD patient subgroups (Figure 3).

DISCUSSION

This study was undertaken to assess the QoL in those pregnant women with or without GERD. We demonstrated that third trimester pregnant women with GERD have worse GH, MH and MCS compared with those pregnant women without GERD. However, in pregnant women with GERD, their educational status was not found to have an impact on their QoL. Additionally, those pregnant women with GERD who had experienced GERD symptoms including heartburn and acid reflux before their pregnancy demonstrated no additional health-related QoL score alterations in their third trimester of pregnancy.

Most pregnant women have symptoms of GERD, including heartburn and regurgitation, due to weakened lower esophageal sphincter and/or the growing uterus, which can put pressure on the stomach. Due to the special conditions of pregnancy, invasive investigations such as esophageal manometry and pH probes to map the gastroesophageal pH gradient are rarely applied, although both of these tests can be safely performed on pregnant women in advanced centers.[15] In general, the diagnosis of GERD in a pregnant woman can reliably be made clinically according to its typical symptoms. In this context, the GERDQ can be used to diagnose GERD with an accuracy comparable to the accuracy of a diagnosis of GERD by a gastroenterologist.

Our analysis emphasizes the importance of clinical conditions on health-related QoL in pregnant women and suggests the need for a

Table 2. Socio-demographic characteristics of study participants

	*Group 1 (n=53), (with GERD)	*Group 2 (n=54), (without GERD)	p
Age (years)	28.0±5.4	27.7±5.4	0.80
Pre-pregnancy BMI in kg/m^2	23.8±4.3	25.2±5.2	0.139
Gravida [median, (minimum-maximum)]	2 (1-6)	2 (1-7)	0.934
Parity [median, (minimum-maximum)]	1 (0-3)	1 (0-2)	0.818
Abortus [median, (minimum-maximum)]	0 (0-3)	0 (0-4)	0.366
Educational status	-	-	0.821
Low (%)	18 (33.9)	18 (33.4)	-
Medium (%)	17 (32.2)	16 (29.6)	-
High (%)	18 (33.9)	20 (37.0)	-
Smoker	-	-	0.76
No (%)	52 (98.2)	52 (96.3)	-
Yes (%)	1 (1.8)	2 (3.7)	-
Prior GERD history	-	-	0.024
No (%)	34 (64.1)	49 (90.8)	-
Yes (%)	20 (35.9)	5 (9.2)	-

BMI: Body mass index, GERD: Gastroesophageal reflux disease, *Group 1: Pregnant cases with GERD, Group 2: Pregnant controls without GERD.

comprehensive medical and social approach for pregnant women with GERD. In clinical practice, QoL assessment has a significant impact on clinically relevant outcomes in healthcare management and clinical research. Different specific and generic instruments are used to evaluate QoL in gastrointestinal disorders during pregnancy but their interrelationship is not well known. SF-36, which was developed as part of the Medical Outcomes Study,[16] is one of the most widely used standardized self-reported assessments which is sufficiently general to be used in various health and disease states including pregnancy.[3,17,18] It is a reliable generic instrument which has 8 scaled scores in which lower scores represent more disability and higher scores represent less disability and better functioning.[16,19]

Although the negative impact of GERD on the QoL of patients has been shown in multiple studies,[20-23] there is scarce data in the literature addressing the effect of GERD on QoL in the advanced stages of pregnancy. In this context, the results of the present study confirmed that GERD in pregnancy significantly impaired the mother's health-related QoL. We demonstrated that, during the third trimester, pregnant women with GERD had significantly decreased QoL in their GH, MH and MH component domains, while no significant changes were observed in the other components of the QoL domains. These alterations, especially in the mental domains, may be explained by the negative influence of the psychological stress induced by GERD. Moreover, complex interactions between biological, environmental, and hormonal factors during pregnancy may be regarded as the predisposing causes of lower QoL scores in these three domains.

One of the key findings of this research was that pregnant women even with or without GERD had mean PCS and MCS scores below 50. It is not surprising to detect a mean PCS or MCS scores below 50 in pregnant women because pregnancy is a condition in which physical activity levels significantly decline. In addition, physical incapacity is a major factor adversely affecting the perceived QoL in pregnancy.[24,25] Although we found low MCS scores in both study groups, the MCS scores of the pregnant women with GERD were statistically lower than the control group. The reason for the lower mean MCS scores in the GERD patients can be attributed to the high levels of psychological stress exacerbated by GERD.

We also revealed that levels of education were not a contributing factor to the QoL scores of the pregnant women. This might be due to the

Table 3. Results of the quality of life (short-form 36) among pregnant women with or without GERD

	*Group 1 (n=53), (with GERD)	*Group 2 (n=54), (without GERD)	p
Physical functioning	55.4±20.9	58.7±21.1	0.419
Role-physical	35.4±35.8	49.7±41.1	0.057
Bodily pain	56.6±23.0	57.2±20.6	0.884
General health	61.3±18.5	72.7±13.8	<0.01
Vitality	49.3±21.8	55.8±18.2	0.097
Social functioning	63.0±23.8	63.1±24.7	0.987
Role-emotional	46.8±32.1	50.6±34.0	0.551
Mental health	58.6±21.7	72.0±13.8	<0.01
Physical component summary	40.6±10.1	42.9±9.80	0.220
Mental component summary	42.7±9.30	46.8±6.70	0.010

GERD: Gastroesophageal reflux disease, *Group 1: Pregnant cases with GERD, Group 2: Pregnant controls without GERD.

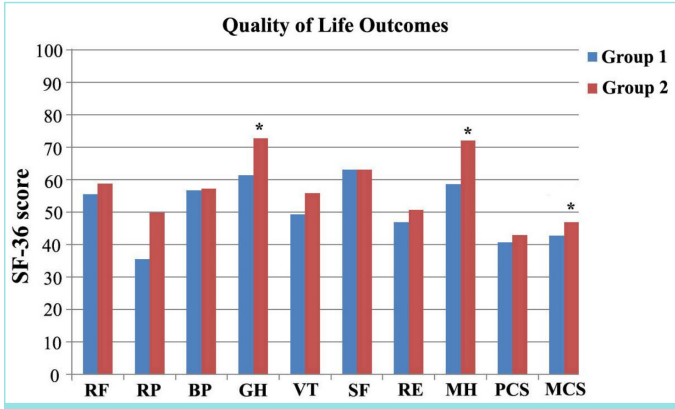

Figure 1. Short-form 36 scores of the pregnant women with GERD (group 1) and without GERD (group 2).

SF-36: Short-form 36, GERD: Gastroesophageal reflux disease, RF: Role functioning, RP: Role-physical, BP: Bodily pain, GH: General health, VT: Vitality, SF: Social functioning, RE: Role-emotional, MH: Mental health, PCS: Physical Health Component Score, MCS: Mental Health Component Score.

Table 4. Results of the quality of life (short-form 36) scores according to the level of education among the pregnant women

	Educational status								
	Low			Middle			High		
	Group 1	Group 2	p	Group 1	Group 2	p	Group 1	Group 2	p
Physical functioning	56.1±19.5	63.8±23.2	0.25	54.7±19.8	67.3±16.1	0.55	57.6±18.9	59.0±24.6	0.84
Role-physical	27.7±34.1	41.7±34.3	0.22	29.3±33.8	36.4±33.3	0.29	29.4±34.5	35.8±35.0	0.57
Bodily pain	57.0±28.6	57.3±18.9	0.96	56.2±28.0	61.4±18.0	0.53	60.4±25.5	53.6±21.6	0.38
General health	62.2±23.4	62.0±12.9	0.97	62.5±22.8	62.8±11.9	0.95	61.4±23.9	61.7±12.7	0.96
Vitality	53.5±20.8	53.7±16.1	0.97	53.9±20.3	53.1±14.9	0.90	54.9±20.6	50.5±17.3	0.48
Social functioning	63.9±27.7	71.9±15.3	0.29	63.8±26.9	73.0±16.4	0.25	66.2±26.8	67.5±18.9	0.85
Role-emotional	45.6±27.3	50.0±33.0	0.66	43.2±28.5	55.6±30.3	0.22	46.3±28.0	44.4±34.0	0.85
Mental health	60.5±20.6	58.2±19.2	0.72	61.1±20.2	60.5±18.6	0.92	61.2±21.0	56.9±18.0	0.51
Physical component summary	42.2±14.2	41.7±7.3	0.88	41.6±14.0	42.0±6.0	0.92	43.1±14.1	40.1±7.8	0.40
Mental component summary	44.0±8.6	43.3±8.0	0.79	44.1±8.3	44.4±7.9	0.89	44.4±8.7	42.3±7.8	0.44

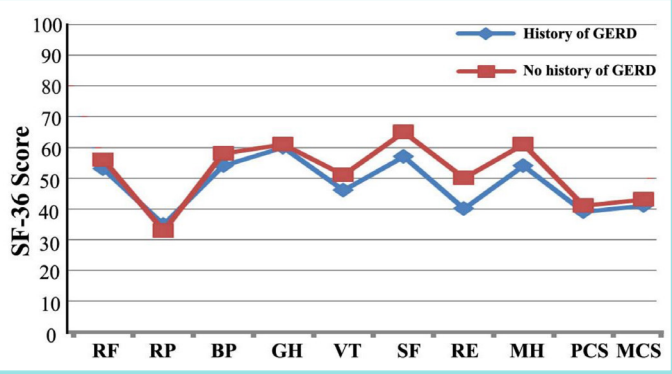

Figure 2. Results of the short-form 36 questionnaire in pregnant women with GERD according to their history of GERD prior to pregnancy.

SF-36: Short-form 36, GERD: Gastroesophageal reflux disease, RF: Role functioning, RP: Role-physical, BP: Bodily pain, GH: General health, VT: Vitality, SF: Social functioning, RE: Role-emotional, MH: Mental health, PCS: Physical Health Component Score, MCS: Mental Health Component Score.

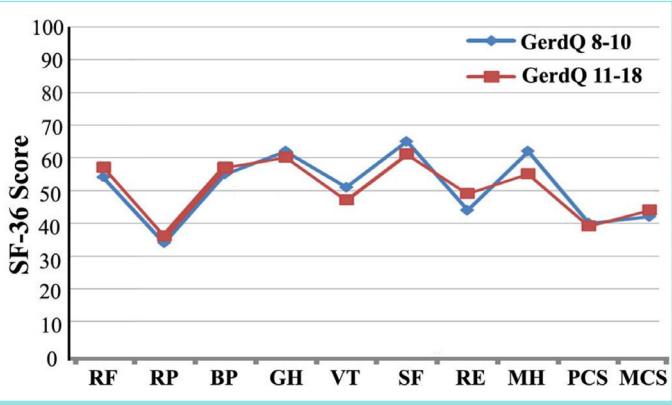

Figure 3. Comparison of the Short-form 36 (SF-36) scores of the pregnant women with GERD according to their GERDQ scores (GERDQ 8-10 vs GERDQ 11-18).

SF-36: Short-form 36, GERD: Gastroesophageal reflux disease, RF: Role functioning, RP: Role-physical, BP: Bodily pain, GH: General health, VT: Vitality, SF: Social functioning, RE: Role-emotional, MH: Mental health, PCS: Physical Health Component Score, MCS: Mental Health Component Score.

already lower QoL scores of the pregnant women, even those with GERD. Furthermore, it can be speculated that the advanced stages of pregnancy which are associated with higher perceived stress leads to restrictions on mental and physical health-related QoL, independent from the educational status of the pregnant women. Contrary to our findings, in a recent study by Barbareschi et al.[26], patients with low educational levels were reported to have worse physical and functional conditions. Similarly, Nicholson et al.[27] reported that not only educational levels but age, marital status and social support during pregnancy might affect the QoL in pregnant women.

Study Limitations

The main limitation of the present study was that the number of patients enrolled was relatively low. A larger sample is required to confirm these results. Moreover it would have been beneficial if we had assessed other factors which could affect QoL in pregnancy, including anxiety and depression.

CONCLUSION

GERD during pregnancy is associated with poor levels of QoL in terms of general and MH. This condition has to be taken into account by those clinicians involved in the care of pregnant women. Further studies are necessary in order to elucidate the factors which contribute to the poor levels of health-related QoL in pregnant women with GERD.

MAIN POINTS

- Gastroesophageal reflux disease significantly affects the quality of life of pregnant women.
- It represents a major healthcare problem due to the high prevalence of gastroesophageal reflux throughout pregnancy.
- In order to improve the quality of life of pregnant women with gastroesophageal reflux disease, a combined health management strategy is needed.

ETHICS

Ethics Committee Approval: Ethical clearance was obtained from Çanakkale Onsekiz Mart University Faculty of Medicine Ethics Board (approval number: 2016-03, date: 17.02.2016).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.B., A.Ç.G., Design: F.B., A.Ç.G., Y.B., Supervision: F.B., M.A.Ü., Data Collection and/or Processing: A.Ç.G., Y.B., Analysis and/or Interpretation: A.Ç.G., M.A.Ü., Literature Search: Y.B., Writing: F.B., M.A.Ü., Critical Review: F.B., M.A.Ü.

DISCLOSURES

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

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REFERENCES

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006; 101(8): 1900-20; quiz 43.
2. Ramu B, Mohan P, Rajasekaran MS, Jayanthi V. Prevalence and risk factors for gastroesophageal reflux in pregnancy. Indian J Gastroenterol. 2011; 30(3): 144-7.
3. Dall'alba V, Callegari-Jacques SM, Krahe C, Bruch JP, Alves BC, Barros SG. Health-related quality of life of pregnant women with heartburn and regurgitation. Arq Gastroenterol. 2015; 52(2): 100-4.
4. Law R, Maltepe C, Bozzo P, Einarson A. Treatment of heartburn and acid reflux associated with nausea and vomiting during pregnancy. Can Fam Physician. 2010; 56(2): 143-4.

5. Charan M, Katz PO. Gastroesophageal Reflux Disease in Pregnancy. Curr Treat Options Gastroenterol. 2001; 4(1): 73-81.

6. Sierżantowicz R, Lewko J, Jurkowska G. The Impact of an Individual Educational Program on the Quality of Life and Severity of Symptoms of Patients with Irritable Bowel Syndrome. Int J Environ Res Public Health. 2020; 17(12): 4230.

7. Revicki DA, Leidy NK, Howland L. Evaluating the psychometric characteristics of the Psychological General Well-Being Index with a new response scale. Qual Life Res. 1996; 5(4): 419-25.

8. Marchesini G, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterology. 2001; 120(1): 170-8.

9. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther. 2009; 30(10): 1030-8.

10. Jemilohun AC, Tijani AM, Fasanu AO. A comparison between the prevalence of gastroesophageal reflux disease among SouthWestern Nigerian pregnant women to that of the nonpregnant ones. Gastroenterology Insights. 2016; 7(1): 6373.

11. María MS, Jaramillo MA, Regino WO, Gomez Zuleta MA. Validation of a questionnaire regarding gastroesophageal reflux (GERD) in a Colombian population. Rev Col Gastroenterol. 2013; 28(3): 199-206.

12. Mungan Z. Prevalence and demographic determinants of gastroesophageal reflux disease (GERD) in the Turkish general population: a population-based cross-sectional study. Turk J Gastroenterol. 2012; 23(4): 323-32.

13. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30(6): 473-83.

14. Koçyiğit H, Aydemir Ö, Fisek G, Ölmez N, Memiş A. The validity and reliability of Turkish version of the Short Form 36 (SF-36). Turkish J Drugs Therap. 1999; 12: 102-6.

15. Al-Amri SM. Twenty-four hour pH monitoring during pregnancy and at postpartum: a preliminary study. Eur J Obstet Gynecol Reprod Biol. 2002; 102(2): 127-30.

16. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994; 32(1): 40-66.

17. Calou C, Pinheiro A, Castro R, de Oliveira M, de Souza Aquino P, Antezana F. Health Related Quality of Life of Pregnant Women and Associated Factors: An Integrative Review. Health. 2014; 6: 2375-87.

18. Lee NM, Saha S. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am. 2011; 40(2): 309-34.

19. Kahrilas PJ, Jonsson A, Denison H, Wernersson B, Hughes N, Howden CW. Impact of regurgitation on health-related quality of life in gastro-oesophageal reflux disease before and after short-term potent acid suppression therapy. Gut. 2014; 63(5): 720-6.

20. Lee SW, Lien HC, Lee TY, Yang SS, Yeh HJ, Chang CS. Heartburn and regurgitation have different impacts on life quality of patients with gastroesophageal reflux disease. World J Gastroenterol. 2014; 20(34): 12277-82.

21. Shirai T, Mikamo M, Tsuchiya T, Shishido Y, Akita T, Morita S, et al. Real-world effect of gastroesophageal reflux disease on cough-related quality of life and disease status in asthma and COPD. Allergol Int. 2015; 64(1): 79-83.

22. Namikoshi T, Harada K, Hatta H, Tokura T, Oshiro Y, Nishizaki T, et al. Prevalence of gastroesophageal reflux disease symptoms and effects of esomeprazole on the quality of life related to reflux and dyspepsia in patients on maintenance hemodialysis. Clin Exp Nephrol. 2016; 20(1): 134-42.

23. Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. Am J Med. 1998; 104(3): 252-8.

24. Atay E, Başalan Iz F. Investigation of the effect of changes in muscle strength in gestational age upon fear of falling and quality of life. Turk J Med Sci. 2015; 45(4): 977-83.

25. Olsson C, Nilsson-Wikmar L. Health-related quality of life and physical ability among pregnant women with and without back pain in late pregnancy. Acta Obstet Gynecol Scand. 2004; 83(4): 351-7.

26. Barbareschi G, Sanderman R, Leegte IL, van Veldhuisen DJ, Jaarsma T. Educational level and the quality of life of heart failure patients: a longitudinal study. J Card Fail. 2011; 17(1): 47-53.

27. Nicholson WK, Setse R, Hill-Briggs F, Cooper LA, Strobino D, Powe NR. Depressive symptoms and health-related quality of life in early pregnancy. Obstet Gynecol. 2006; 107(4): 798-806.

RESEARCH ARTICLE

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Spinal Cord Stimulation and YouTube: Content Analysis of Online Health Information

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Abstract

BACKGROUND/AIMS: Spinal cord stimulation (SCS) is a highly specialized and complex therapeutic method which uses an implanted device to personalize pain control. The main pur-pose of this study was to evaluate the quality, reliability, and sufficiency of the most viewed YouTube videos regarding SCS.

MATERIALS AND METHODS: This study provides a descriptive analysis of YouTube videos with the keywords "SCS", "SCS implantation", "SCS risks", or "SCS benefits". The Global Quality Score (GQS), the Journal of American Medical Association Benchmark Criteria (JAMA) and the Modified DISCERN Questionnaire (mDISCERN) scales were used to assess the videos' level of quality, reliability, and sufficiency.

RESULTS: A total of 63 videos were evaluated. The median score for GQS was 3 (1-5), while that for JAMA and mDISCERN was 2 (1-4) and 2 (0-5), respectively. While approxi-mately half of the videos (46%, n=29) were of poor-quality, the majority of the videos (65%, n=41) had partially adequate data. The video length and days posted for those videos with high-quality were significantly shorter than those for videos with either poor or intermediate quality ($p=0.03$, $p<0.001$).

CONCLUSION: YouTube offers easy access to medical information about SCS, however, videos about SCS were mostly partially inadequate and of moderate quality. Our results showed that YouTube is currently not a suitable online platform for patients. Patient information videos should only be created and disseminated by professional medical societies and monitoring standards are needed.

Keywords: Internet, online health information, social media, spinal cord stimulation, YouTube

INTRODUCTION

Spinal cord stimulation (SCS) is an emerging, minimally invasive intervention in the treatment of chronic neuropathic pain. SCS delivers electrical pulses directly to the spinal cord in order to inhibit the transmission of pain signals to the brain.[1] Each year, approximately 50,000 patients worldwide undergo SCS for indications such as failed back surgery syndrome, diabetic neuropathy, or complex regional pain syndrome, with varying degrees of success.[2,3] Being the most common neuromodulation therapy, its use has increased over the past decade and it is recommended in international clinical guidelines in Europe and the USA.[4,5] More recent technologies have now been developed, many of which avoid paresthesia.[6] SCS provides personalized pain control and optimization of its management at an individual patient level and therefore requires collaboration with the patient.

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The internet has revolutionized the world and resulted in innovative advances in the education and dissemination of medical information. It has become one of the most important sources of information for health issues with the capacity to rapidly sort through a huge amount of information. YouTube is a popular video site with over 1 billion users and over 5 billion visitors per day and it is considered to be an important medical information source today.[7] The ubiquity of YouTube has made it an educational resource for patients and a visual educational guide for medical professionals.

Among the interventional pain treatment approaches, SCS is a highly specialized and complex treatment modality which personalizes pain control with an implanted device, therefore, individuals can be unfamiliar with the benefits or complications of SCS. In general, patients may request information on SCS from their physicians, but previous research revealed that informed consent for surgical procedures, the critical component of interventional practice, is often incomplete.[8,9] Consequently, at least 74% of internet users search for medical information, which later influences their medical decision-making, with YouTube being one of the most popular platforms to access such information.[10,11] The internet can increase social support among patients, promote their sense of autonomy and individual decision-making, and also allow access to patient experiences and the views of other medical professionals. However, there is still no standard for quality control of medical content on online platforms. It is still a major problem that unregulated, low-quality, or inaccurate healthcare information is widely available.[12,13] Misleading or inappropriate information can put patients at risk and adversely affect their decision-making process.

In the practice of pain medicine, it is vital to provide clear visual guidance in order to define the complex interactions of anatomical structures, clinical skills, and medical knowledge. Several pain medicine organizations regularly produce comprehensive educational multimedia materials for advanced invasive interventions such as the SCS procedure. Recently, YouTube has become a potentially useful source of medical information for healthcare professionals, as they can easily access information about this complex condition relayed through a basic visual format. However, there is currently a risk that medical information on YouTube may be displayed in a way that is inaccurate, disorganized, or unfiltered.[12,13] Therefore, strategies should be implemented in order to evaluate and regulate YouTube videos.

Our primary aim was to evaluate the quality, reliability, and sufficiency of YouTube videos which patients and healthcare professionals encounter when using the internet for information regarding SCS. Our secondary aims were to evaluate the YouTube characteristics and production sources of SCS-related videos.

MATERIALS AND METHODS

1. Study Design and Ethics

This study provides a descriptive analysis of internet searches, without involving any experimental humans or animals. As a result, since the evaluated data were readily available to the public, this study did not need ethics committee permission.

We selected the search terms by using the Google Trends tool, which indicated the most popular search keywords by determining their search frequency related to the total worldwide traffic and by discussion among the authors of this study. After accessing YouTube with the Mozilla Firefox browser, we searched for the keywords "SCS", "dorsal column stimulation", "SCS implantation", "SCS risks", and "SCS benefits" using the private window settings. Private window mode provides users with an online privacy feature which disables the user's browsing history and the collection of individualized search results. Private window mode restricts the potential of encountering altered search algorithms. Relevance-based sequencing determined by internal YouTube algorithms was performed to sort the videos. The ranking of videos on YouTube may change due to changes in their number of views or their relevance. Therefore, the search results were compiled in a single session, on 01.09.2022. Since our aim was not to evaluate all videos, but only those most likely to be clicked on by internet users, we performed our evaluation on the top 50 videos alone. The exclusion criteria were; non-English videos, unrelated videos, and advertisements. Duplicate or inaccessible videos were also eliminated. The inclusion criteria were; mainly SCS-related content, English language, and real patients' experiences. In the final assessment, the videos were categorized into four groups; videos created by health care professionals, medical organizations or associations were classified as "*medical*", videos edited by public associations or media organizations were classified as "*non-medical*", and also videos were classified as being of "*patient origin*" or "*SCS device manufacturer origin*".

2. Video Characteristics

The following parameters of the videos included were evaluated; country of origin, total viewership, number of likes and dislikes, number of comments, days since being posted, and the length of the video (seconds). Also, their view ratio (the number of views/number of days x100%), and the video interaction index (number of likes & dislikes x the number of views/100%) were calculated from the metadata of the videos.

3. Video Assessment

The top 50 videos for each term were assessed by the one of the authors, and the links were shared with the three investigators who rated the videos. Three pain specialists were selected as the assessor team. If there was a major differences in the ratings between the assessors, consensus was made to reach a final decision. If uncertainties about the videos could not be resolved, a voting method was performed to obtain a score for those videos. The following tools were used to determine the reliability, accuracy and quality of the video-based information on SCS; the Global Quality Score (GQS) and Journal of the American Medical Association (JAMA) Benchmark Criteria, and the Modified DISCERN Questionnaire.

3.1. Global Quality Score

The GQS instrument with a scale of 1 to 5 was used to assess the videos' content quality, including the flow of the videos and the accuracy of their content. The information was categorized in the GQS as follows: it is of poor-quality with a poor flow, and has the majority of information missing, making it useless to patients (1); it is generally poor, has some information provided but very limited usefulness for patients (2); it is of moderate-quality and discusses some important information adequately (3); it is of good-quality and has most of the information listed, and so is useful for patients (4); or it is of excellent-quality and has very good flow, making it very useful (5). Information with a higher GQS is of higher-quality. Bernard et al.[14] created this scale to assess how easily accessible and logically organized information on websites is.

3.2. JAMA Benchmark Criteria

The reliability and accuracy of videos and resources were evaluated using the JAMA, a 4-point tool. Their authorship, attribution, disclosure, and currency are the four classifications.[15] Each video was evaluated by an examiner, who assigned one score for each category.

3.3. Modified DISCERN Questionnaire

There are five *yes/no* questions on the Modified DISCERN Questionnaire's score scale. These questions look at the features of the resources in order to assess their quality. The overall score was determined by adding the "*yes*" scores, which are worth one point per score and so there is a possible range from 0 to 5, with 5 being the highest resource quality.[16,17]

Statistical Analysis

SPSS 16.0 Statistical package program (SPSS, Chicago, IL, USA) was used for statistical analysis. Quantitative variables were tested for normality using the Shapiro-Wilk test. Descriptive data were presented as numbers (n), frequencies (%), medians, minimums and maximums. Non-parametric data was compared using Kruskal-Wallis with post-hoc Bonferroni correction for multiple comparisons. Spearman correlation was performed in order to assess any association of the video assessment scores (GQS, JAMA and Modified DISCERN) with the video parameters. A p-value <0.05 was considered to be statistically significant.

RESULTS

A total of 63 videos were analyzed. The flowchart for the video selection is demonstrated in Figure 1. Most of the videos were posted from the US (87.3%, n=55), and the video uploaders were mainly professional health organizations (46.03%, n=29). Table 1 shows the descriptive information regarding the videos.

The median scores for GQS, JAMA and Modified DISCERN Questionnaire (mDISCERN) were 3 (1-5), 2 (1-4) and 2 (0-5), respectively. Based on the GQS, 21 of 63 videos were classified as being of high-quality, while approximately half of the videos (29/63) were categorized as poor-quality. The majority of the videos (65.1%, n=41) had only partially adequate data (i.e., 2 or 3 points on the JAMA scale). Table 2 shows the assessment of the medical content.

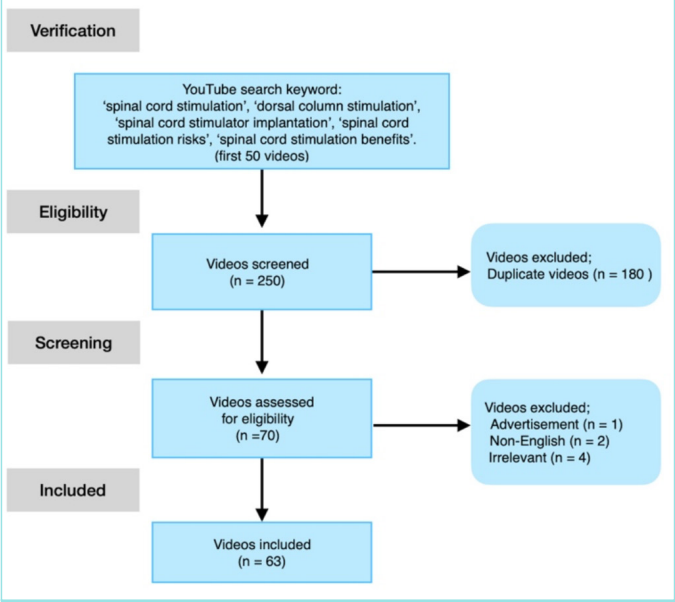

Figure 1. Flow chart of the selection of the videos.

According to a comparison of video quality with the GQS, the video length for those videos with high content quality was significantly shorter than for those videos with either poor content quality or moderate content quality, (p=0.03). Additionally, high content quality videos had been posted more recently to the network than those videos with either poor or moderate content quality (p<0.001). Comparisons of the assessment scores based on the GQS are shown in Table 3.

Table 1. Descriptives of the YouTube videos regarding SCS

	Total (n=63)
Country of origin	
U.S.A.	55 (87.3%)
U.K.	3 (4.7%)
Canada	3 (4.7%)
India	2 (3.1%)
Number of views	7,683 (277-372,713)
Length of video (seconds)	249 (77-2,976)
Likes	41 (0-1,714)
Dislikes	3 (0-119)
Comments	0 (0-1,418)
Days since being posted	987 (54-4,922)
Viewing numbers	8.21 (0.08-362.4)
Interaction index	0.63 (0-5.44)
GQS	3 (1-5)
JAMA	2 (1-4)
mDISCERN	2 (0-5)

Data are presented as number (%) or median (minimum-maximum). SCS: Spinal cord stimulation, U.S.A.: United States of America, U.K.: United Kingdom, GQS: Global Quality Score, JAMA: Journal of American Medical Association Benchmark Criteria, mDISCERN: Modified DISCERN Questionnaire.

Table 2. Assessment of medical content

GQS	
Poor-quality (1-2 points)	29 (46)
Moderate-quality (3 points)	13 (20.6)
High-quality (4-5 points)	21 (33.3)
JAMA	
Inadequate data (1 point)	20 (31.7)
Partially adequate data (2-3 points)	41 (65.1)
Completely adequate data (4 points)	2 (3.2)
mDISCERN	
0	4 (6.3)
1	10 (15.9)
2	20 (31.7)
3	17 (27)
4	10 (15.9)
5	2 (3.2)

Data are presented as number (%). GQS: Global Quality Score, JAMA: Journal of American Medical Association Benchmark Criteria, mDISCERN: Modified DISCERN Questionnaire.

When comparing the videos in terms of their sources, the median GQS, JAMA and mDISCERN scores of those videos uploaded by medical organizations were higher than those videos uploaded by patients or non-medical media organizations ($p<0.001$). The GQS, JAMA, and DISCERN scores for videos uploaded by either patients or non-medical organizations were found to be lower than those uploaded by SCS device manufacturers ($p<0.001$). The video lengths for those videos uploaded by medical organizations or health care professionals were significantly longer compared to those of non-medical organizations ($p=0.028$) (Table 4).

A significant negative correlation was present between the number of days since being posted and the content quality. Those videos with high-quality had been uploaded more recently than those with poor or moderate content quality ($r=-0.654$; $p<0.001$) (Table 5).

DISCUSSION

In this study, we assessed the accuracy, reliability and quality of the most popular YouTube videos providing information about SCS. According to GQS, approximately half of the videos were in the poor-quality group, and most videos had partially adequate data based on their JAMA scores. Additionally, in terms of GQS, videos in the high content quality group were associated with shorter video length, fewer days since uploading, higher JAMA and mDISCERN scores. Our results also demonstrated that the quality, accuracy, and reliability of those videos created by patients were lower than those uploaded by either medical organizations, health care professionals, or SCS device manufacturers.

YouTube is the most widely used video hosting platform, as well as the second most clicked on site globally.[18] Although YouTube was not created for the dissemination of online health information or medical education, the internet revolution has had an impact on online health platforms, making it one of the most popular sources of health data. Currently, video-based learning has become one of the most important learning methods. Recently, several studies have reported on the benefits of video-based learning in the learning process, particularly in increasing the understanding of information.[19-21] Other advantages of video-based learning are that it takes less time, it is easily accessible at any time, and it has reusable resources. Moreover, studies indicate that online written content provided by professional organizations and medical health information websites exceed the health-literacy policies recommended by guidelines.[22] Unlike written-format information, YouTube videos have the advantages of translating complex medical terminology into simpler terms, allowing audiences to easily understand the subject. However, there is no peer-review process or quality control standard for YouTube videos, giving the public access to unfiltered, often inaccurate information, which can adversely affect

Table 3. Parameters of YouTube™ videos regarding Global Quality Score

Factor	Poor-quality	Moderate-quality	High-quality	p[a]
Number of views	7,683 (277-199,959)	11,137 (775-372,713)	3,721 (310-117,095)	0.146
Days since being uploaded	1,436 (200-4,922)	1,460 (203-3,792)	478 (54-1,001)[c,d]	<0.001
Length of video (seconds)	210 (77-2,766)	292 (106-2,309)	384 (143-2,976)[c,d]	0.03
Number of comments	3 (0-1,418)	0 (0-469)	0 (0-340)	0.098
Interaction index	0.607 (0-5.44)	0.69 (0.02-1.94)	0.859 (0-1.85)	0.871
Viewing rate	6.576 (0.08-139.25)	10.015 (3.82-362.4)	9 (0.6-99.32)	0.126
JAMA score	1 (1-3)	2 (2-3)[b]	3 (2-4)[c]	<0.001
mDISCERN score	2 (0-2)	3 (2-3)[b]	4 (2-5)[c]	<0.001

Data are presented as median (minimum-maximum). Note that Bonferroni adjustment was done. [a]Kruskal-Wallis test was performed. [b]Pairwise comparison between poor-quality and moderate quality videos. [c]Pairwise comparison between poor-quality and high-quality videos. [d]Pairwise comparison between moderate-quality and high-quality videos (adjusted p-values <0.05 for pairwise comparisons between groups). JAMA: Journal of American Medical Association Benchmark Criteria, mDISCERN: Modified DISCERN Questionnaire.

Table 4. Comparison of parameters according to the source of the YouTube videos

Factor	Medical	Non-medical media organization	Patient	Manufacturer	p[a]
Number of views	11,137 (310-372,713)	7,683 (713-110,045)	9,273 (3,530-86,637)	3,698 (277-254,407)	0.087
Length of the video (seconds)	377 (146-2,766)[b]	180 (77-244)	417 (93-2,976)	248 (94-1140)	0.028
Days since being uploaded	1,436 (72-3,792)	1,042 (200-2,001)	1,181 (595-4,922)	702 (54-3,665)	0.093
Interaction index	0.55 (0-1.67)	0.773 (0.2-3.23)	0.685 (0.06-5.44)	0.637 (0-1.85)	0.372
Viewing rate	10.01 (0.44-199.38)	4.87 (1.36-79.28)	7.75 (0.72-52.25)	8.69 (0.08-362.4)	0.285
GQS	3 (1-5)[b,c]	2 (1-3)	2 (1-2)	3 (1-4)[f,g]	<0.001
JAMA	3 (1-4)[b,c]	1 (1-2)	1 (1-2)	3 (1-3)[f,g]	<0.001
mDISCERN	3 (1-5)[b,c]	2 (0-2)	1 (0-2)	3 (1-4)[f,g]	<0.001

Data are presented as median (minimum-maximum). Note that Bonferroni adjustment was performed. [a]Kruskal-Wallis test was performed. [b]Pairwise comparison between medical vs. non-medical media organization videos. [c]Pairwise comparison between medical vs. patient videos. [d]Pairwise comparison between the medical vs. manufacturer videos. [e]Pairwise comparison between the non-medical media organization vs. patient videos. [f]Pairwise comparison between the non-medical media organization vs. manufacturer. [g]Pairwise comparison between the patient vs. manufacturer (adjusted p-values <0.05 for pairwise comparisons between groups). GQS: Global Quality Score, JAMA: Journal of American Medical Association Benchmark Criteria, mDISCERN: Modified DISCERN Questionnaire.

the perceptions and decision-making processes of the patients and their families. Moreover, video-sharing platforms including YouTube have positioned themselves as an important way to access up-to-date medical information for healthcare professionals. Therefore, it might be beneficial for medical professionals to read research regarding these videos and learn about the parameters of their quality. Therefore, we aimed to evaluate YouTube's current SCS content in this study.

According to the results of this study, patients and healthcare professionals may face difficulties in accessing trustworthy and useful information regarding SCS presented on YouTube. According to the GQS, only about one-third of the videos had high-quality, and only two of the videos fulfilled all JAMA criteria for assessing quality and reliability. Supportively, many previous studies evaluating medical information regarding topics such as vaccinations, deep brain stimulation and disc herniation, reported YouTube videos to be of low-quality and reliability.[23-25] As one of the core aspects of interventional pain procedure training is visual in nature, the use of videos for pain medicine practice can be crucially beneficial for trainees. How to produce reliable and high-quality visual materials and incorporate them into pain medicine practice is in itself an important topic for pain medicine. Therefore, high accuracy and quality videos produced for use in pain medicine practice require extensive planning and careful execution.

One of the most striking points in this process of reviewing YouTube videos was the inadequate performance of the video content in reporting the complications and risks of SCS. It is important to provide accurate and unbiased information to patients scheduled for SCS during their decision-making process. In this process, when discussing the significance of SCS, its benefits and the rationale for its use are prioritized in most videos, however, the risks of this procedure and the life modifications after SCS implantation, although rare, were less shared. Indeed, SCS is a highly specialized and complex treatment modality which personalizes pain control with an implanted device, and individuals may not be adequately informed about its benefits, complications or outcomes. Newer technologies have now been produced, many of which are paresthesia-free.[26] Given that paresthesia can cause some discomfort, especially with positional changes and in a variety of activities, paresthesia-free SCS could be an option for patients.[27] Thus, patients who are candidates for SCS go looking for information regarding SCS, and the internet is the easiest way to access this knowledge. The mDISCERN subscale of "uncertainty" and GQS assessing video content could be valuable items for patients researching information for their decision-making process. It is important to provide patients with reliable and clear information about the various aspects of SCS, such as the trial and implantation phases, its complications and risks, the variable degrees of success in different neuropathic pain syndromes, and its mechanism of action. Unbiased videos can assist patients to distinguish well-known facts from unproven and unclear areas.

Of the 63 videos included in our study, 12 (19%) were "*patient*" videos, which are real patient experiences or opinions about SCS. This finding indicates that patients use the internet not only to research health information, but also to disseminate medical information. In general, patient experiences may provide beneficial information for prospective patients seeking real-life opinions about SCS. However, the perspective of patients who have undergone SCS could be significantly biased and adversely affect the perceptions of prospective patients and this can lead to the spread of unfiltered, often inaccurate information. Our study found that the quality, accuracy, and reliability of videos produced by patients were lower than that of videos produced by SCS device manufacturers and medical organizations. This finding is consistent with a wealth of literature indicating that the source of videos is related to its content quality. The quality of videos shared by non-medical users was lower than those of professional healthcare uploaders or medical organizations.[28-30] Our results suggest that before viewing a video about SCS, one should consider the source of the video. Online health information videos should only be produced and posted by reputable professional societies and qualified specialists in order to avoid the spread of unregulated low-quality or inappropriate information. Furthermore, the patients' capability to understand medical information will be affected by their level of health literacy and the complexity of the terminology used. Although this subject may appear contradictory, meeting certain standards and providing complex information in a direct manner by expert authors will allow the general public to receive reliable medical information.

Table 5. Correlations between parameters and assessment scores of the YouTube videos about SCS

Factor	GQS score	JAMA score	mDISCERN score
View number	r=-0.114	r=-0.174	r=-0.039
Days since being uploaded	r=-0.654; p<0.001	r=-0.447; p<0.001	r=-0.471; p<0.001
Length of the video (seconds)	r_s=0.309; p<0.014	r_s=0.254; p=0.045	r_s=0.295; p=0.019
Number of comments	r=0.125	r=0.035	r=0.043
Interaction index	r=0.147	r=-0.017	r=0.014
Viewing rate	r=0.169	r=0.181	r=0.171
GQS	-	r=0.812; p<0.001	r=0.883; p<0.001
JAMA	r=0.812; p<0.001	-	r=0.716; p<0.001
mDISCERN	r=0.883; p<0.001	r=0.716; p<0.001	-

P: Results of Spearman rank correlation (r_s) test. GQS: Global Quality Score, JAMA: Journal of American Medical Association Benchmark Criteria, mDISCERN: Modified DISCERN Questionnaire.

After categorizing videos according to the GQS as poor, moderate or high-quality, we found that high content quality videos had longer durations. This finding was mainly secondary to the fact that longer videos had the potential to be better organized with a clearer plan and that a longer video durations provided the opportunity to deliver more rounded evaluations of SCS. A negative association was present between the quality of the videos and the number of days since its uploading, namely, videos with high content quality had been uploaded more recently. However, there were no differences in the interaction index or viewing rates between videos of different levels of quality, which is of great concern. Similar findings were reached in previous studies, namely that the number of likes, dislikes or views was not a prognostic factor for identifying high-quality videos.[31,32] These results indicate that patients are unlikely to understand the quality of information presented on YouTube and that low-quality content videos containing misleading information are watched as often as high-quality videos.

Study Limitations

This study had a few limitations. Firstly, the evaluation was completed on a single day, but YouTube is a dynamic platform, so the parameters of videos may vary over time. Secondly, only videos in English were included. However, English is a global language, and English-language information may be accessed from anywhere in the world. Finally, since there are other online platforms besides YouTube that patients can use to research information, further studies assessing and comparing these platforms should be planned.

CONCLUSION

The results of this present study demonstrated that videos about SCS on YouTube mostly contained partially sufficient data and about half of the videos had poor content quality. Also, according to our results, the reliability, accuracy and quality scores of those videos published by medical organizations were higher than those uploaded by patients or non-medical media organizations. Finally, we believe that the results of this present study will draw attention to the lack of trustworthy information on SCS and motivate professional societies to improve the quality of online health information. Effective and comprehensible information retrieval may improve perceptions among the public towards SCS.

MAIN POINTS

- With its ability to quickly search through a vast amount of information, the internet has become as one of the most significant sources of information for health-related issues.
- SCS is one of the interventional pain treatment methods which personalizes pain control with an implanted device; as such, people may not be familiar with the advantages or disadvantages of SCS.
- The Internet can allow patients to feel more supported by their social networks, encourage their sense of independence and their ability to make their own decisions, and give them access to other patients' experiences and the opinions of other medical professionals.
- The results of this present study will draw attention to the lack of reliable information about SCS on YouTube, and motivate professional societies to improve the quality of online health information.

ETHICS

Ethics Committee Approval: As a result, since the evaluated data were readily available to the public, this study did not need ethics committee permission.

Informed Consent: It wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.C.K., S.T., Ö.T.A., Design: H.C.K., S.T., Ö.T., Ö.T.A., Data Collection and/or Processing: S.G.K., H.C.K., Ö.T., Ö.T.A., Analysis and/or Interpretation: H.C.K., S.T., Literature Search: S.G.K., H.C.K., Ö.T., Writing: S.G.K., H.C.K., F.Ç.

DISCLOSURES

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

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REFERENCES

1. Sdrulla AD, Guan Y, Raja SN. Spinal Cord Stimulation: Clinical Efficacy and Potential Mechanisms. Pain Pract. 2018; 18(8): 1048-67.
2. Sun L, Peng C, Joosten E, Cheung CW, Tan F, Jiang W, et al. Spinal Cord Stimulation and Treatment of Peripheral or Central Neuropathic Pain: Mechanisms and Clinical Application. Neural Plast. 2021; 2021: 5607898.
3. Aarabi B. Personalising pain control with spinal cord stimulation. Lancet Neurol. 2020; 19(2): 103-4.
4. Cruccu G, Simpson BA, Taylor RS. 56 EFNS guidelines on spinal cord stimulation for neuropathic pain. Eur J Pain. 2007; 11(S1): S22.
5. North R, Shipley J, Prager J, Barolat G, Barulich M, Bedder M, et al. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. Pain Med. 2007; 8(Suppl 4): S200-75.
6. London D, Mogilner A. Spinal Cord Stimulation: New Waveforms and Technology. Neurosurg Clin N Am. 2022; 33(3): 287-95.
7. Baran C, Yilmaz Baran S. Youtube videos as an information source about urinary incontinence. J Gynecol Obstet Hum Reprod. 2021; 50(10): 102197.
8. D'Souza RS, Johnson RL, Bettini L, Schulte PJ, Burkle C. Room for Improvement: A Systematic Review and Meta-analysis on the Informed Consent Process for Emergency Surgery. Mayo Clin Proc. 2019; 94(9): 1786-98.
9. Hanson M, Pitt D. Informed consent for surgery: risk discussion and documentation. Can J Surg. 2017; 60(1): 69-70.
10. Internet Usage Statistics [Internet] Avaible at: http://www.internetworldstats.com/stats.htm Accessed September 10, 2022.
11. D'Souza RS, D'Souza S, Strand N, Anderson A, Vogt MNP, Olatoye O. YouTube as a source of medical information on the novel coronavirus 2019 disease (COVID-19) pandemic. Glob Public Health. 2020; 15(7): 935-42.
12. Steinberg PL, Wason S, Stern JM, Deters L, Kowal B, Seigne J. YouTube as source of prostate cancer information. Urology. 2010; 75(3): 619-22.
13. Sharma R, Lucas M, Ford P, Meurk C, Gartner CE. YouTube as a source of quit smoking information for people living with mental illness. Tob Control. 2016; 25(6): 634-7.
14. Bernard A, Langille M, Hughes S, Rose C, Leddin D, Veldhuyzen van Zanten S. A systematic review of patient inflammatory bowel disease information resources on the World Wide Web. Am J Gastroenterol. 2007; 102(9): 2070-7.

15. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet: Caveant lector et viewor--Let the reader and viewer beware. JAMA. 1997; 277(15): 1244-5.

16. Singh AG, Singh S, Singh PP. YouTube for information on rheumatoid arthritis--a wakeup call? J Rheumatol. 2012; 39(5): 899-903.

17. Charnock D, Shepperd S, Needham G, Gann R. DISCERN: an instrument for judging the quality of written consumer health information on treatment choices. J Epidemiol Community Health. 1999; 53(2): 105-11.

18. Statista. Most popular websites worldwide as of June 2022, by total visits (in billions). [Internet]. New York (NY): Statista Inc.; 2021. (Accessed: September 10, 2022). Available at: https://www.statista.com/statistics/1201880/most-visited-websites-worldwide/

19. Curran V, Simmons K, Matthews L, Fleet L, Gustafson DL, Fairbridge NA, et al. YouTube as an Educational Resource in Medical Education: a Scoping Review. Med Sci Educ. 2020; 30(4): 1775-82.

20. Zhang K, Chao WL, Sha F, Grauman K. Video summarization with long short-term memory. Proc. Eur. Conf. Comput. Vision. 2016.p.766-82.

21. Selvi O, Tulgar S, Senturk O, Topcu DI, Ozer Z. YouTube as an informational source for brachial plexus blocks: evaluation of content and educational value. Braz J Anesthesiol. 2019; 69(2):168-76.

22. Guven Kose S, Kose HC, Erbakan M, Tulgar S. Brain death and the internet: evaluating the readability and quality of online health information. Minerva Anestesiol. 2022; 88(9): 698-705.

23. Keelan J, Pavri-Garcia V, Tomlinson G, Wilson K. YouTube as a source of information on immunization: a content analysis. JAMA. 2007; 298(21): 2482-4.

24. Gokcen HB, Gumussuyu G. A Quality Analysis of Disc Herniation Videos on YouTube. World Neurosurg. 2019: S1878-8750(19)30246-3.

25. Ward M, Abraham ME, Craft-Hacherl C, Nicheporuck A, Ward B, Pashkhover B, et al. Neuromodulation, Deep Brain Stimulation, and Spinal Cord Stimulation on YouTube: A Content-Quality Analysis of Search Terms. World Neurosurg. 2021; 151: e156-62.

26. Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, et al. Neuromodulation for chronic pain. Lancet. 2021; 397(10289): 2111-24.

27. Sweet J, Badjatiya A, Tan D, Miller J. Paresthesia-Free High-Density Spinal Cord Stimulation for Postlaminectomy Syndrome in a Prescreened Population: A Prospective Case Series. Neuromodulation. 2016; 19(3): 260-7.

28. Altun A, Askin A, Sengul I, Aghazada N, Aydin Y. Evaluation of YouTube videos as sources of information about complex regional pain syndrome. Korean J Pain. 2022; 35(3): 319-26.

29. Şahin A, Şahin M, Türkcü FM. YouTube as a source of information in retinopathy of prematurity. Ir J Med Sci. 2019; 188(2): 613-7.

30. Tolu S, Yurdakul OV, Basaran B, Rezvani A. English-language videos on YouTube as a source of information on self-administer subcutaneous anti-tumour necrosis factor agent injections. Rheumatol Int. 2018; 38(7): 1285-92.

31. MacLeod MG, Hoppe DJ, Simunovic N, Bhandari M, Philippon MJ, Ayeni OR. YouTube as an information source for femoroacetabular impingement: a systematic review of video content. Arthroscopy. 2015; 31(1): 136-42.

32. Li M, Yan S, Yang D, Li B, Cui W. YouTube™ as a source of information on food poisoning. BMC Public Health. 2019; 19(1): 952.

RESEARCH ARTICLE

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An Experimental Study in an Induced Lung Injury Model in Sheep to Test a Novel Compression Ventilator

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Abstract

BACKGROUND/AIMS: In a critical care setting, a simple, non-complex but reliable mechanical ventilator would serve as a candidate device in saving human life and qualified medical resources. In this study, we aimed to evaluate the efficacy, safety and reliability of a novel simple mechanical ventilator (ASC-1) developed for ventilation in an induced lung injury model and to compare the normal physiologic lung condition with an induced pathologic lung condition in sheep.

MATERIALS AND METHODS: A sheep ventilation model was established in three female sheep which were anesthetized and intubated. Sheep A was ventilated with a conventional mechanical ventilator, Sheep B was ventilated with ASC-1 accordingly to the protective ventilation protocols. The lung injury model was induced with saline lavage in Sheep C. Following this, the animal was ventilated with ASC-1. At the end of 12 hours, the sheep were euthanized under anesthesia. The vital signs and changes in their arterial blood gas (ABG) were recorded.

RESULTS: The biopsies collected from lungs were examined histologically. The injury and ventilation status of the lungs were examined radiographically. During the ventilation, all sheep maintained stable fluid-electrolyte balance and ABG, and no catastrophic events occurred in any of the sheep. The respiratory parameters of Sheep A were stabilized easily with an intensive care unit ventilator. Additionally, the parameters of Sheep B and Sheep C were also stabilized with the ASC-1 ventilator, at least clinically. The histological findings of the tissues were comparable between the three sheep.

CONCLUSION: As a safe, reliable, low-cost ventilator, the ASC-1 ventilator may be a good alternative to be used in critical respiratory care per se, resulting in no further lung damage, especially in pandemic conditions where shortages of ventilators may be problematic.

Keywords: Critical care, mechanical ventilation, animal model, sheep, lung injury

INTRODUCTION

Mechanical ventilation is one of the most common interventions implemented in critical respiratory care. More than half of the patients in the intensive care unit (ICU) are ventilated within the first 24 hours after ICU admission. These patients are comprised of individuals who have acute respiratory failure, compromised lung function, difficulty in breathing, or failure to protect their airway.[1] There are multiple modes of mechanical ventilation support which provide air to the patient based on pressure, flow and volume. In spite of being lifesaving, mechanical

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ventilation can be associated with life threatening complications, including air leaks and pneumonia.[2]

In the era of the coronavirus disease-2019 (COVID-19) outbreak, each medical facility is concerned about shortages of mechanical ventilator supplies. Stockpiling these sophisticated, expensive intensive care ventilators during pre-pandemic periods is not a feasible solution. Even well-developed countries which have an adequate number of commercial, technical and industrial resources for these medical devices are confronted with these limitations in the fight against COVID-19.[3] Therefore, an adequate number of affordable, easy-to-use, safe and efficient ventilators are urgently needed in ICUs.

Commonly used to provide positive pressure ventilation in the treatment of the respiratory failure, bag valve masks (BVMs) are hand-held, low-cost, easily attainable and simple medical devices. However, this successful system has certain shortcomings, resulting in several complications during ventilation. Manual ventilation of the intubated patients requires the physical effort of the operator as well as the operator's full attention on the procedure.[4] Moreover, it is challenging to verify whether the precise volume of air is being delivered during ventilation since the delivered volume depends on the method of squeezing. Additionally, the tidal volumes typically delivered using adult BVMs are often higher than the recommended volumes for lung protective ventilation protocols.[5] Unfortunately, healthcare professionals tend to cause hyperventilation when using the current BVM devices, which could have detrimental effects on the respiratory and cardiovascular physiology.[6] Therefore, overcoming the shortcomings of these of BVMs with the assistance of an alternative affordable device can provide opportunities in facilitating respiratory care.

One of BVM compression ventilators, the ASC-1, is a novel low-cost simple mechanical ventilator which is manufactured for ventilatory support and offers a favorable alternative when a conventional ICU ventilator is not available for intervention on respiratory failure patients. It also allows the clinician to control the tidal volume, the inspiratory pressure, the respiratory rate and the inspiratory/expiratory (I/E) ratio and to support positive end expiratory pressure (PEEP) and peak airway pressure monitoring, by integrating the filtration and plumbing with filters and suitable breathing systems (Figure 1). In the present observational experimental study, we aimed to evaluate the efficacy, safety and reliability of this novel ventilator (ASC-1), which was developed for mechanical ventilation, in an induced lung injury model, and to compare the normal physiologic lung condition with an induced pathologic lung condition in sheep.

MATERIALS AND METHODS

Animals

The study protocol was approved by the Committee of the Near East University for the Animal Care and Use (approval number: 2020/116, date: 20.05.2020). Patient approval has not been obtained as it is performed on animals. All protocols were in accordance with the National Laboratory Animals Care Guidelines. Three female sheep (*Ovis aries*) weighing between 50-65 kg were supplied by Near East University Havva Hanım Practice and Research Farm. Before the procedures, the sheep were examined by a veterinarian physically and all laboratory testing was performed. The selection criteria of the sheep were their comparable lung sizes to an adult human lung and comparable respiratory physiology to human respiratory physiology.[7]

One day before the experiment, the sheep were transferred from the farm and maintained in the Faculty of Veterinary Medicine of Near East University, in livestock pens with free access to food and water in a covered area at 20-22 °C and 12:12 light/dark cycle. The animals fasted for 10 hours before the study but they were allowed to drink water.

Anesthesia Protocol

The sheep were sedated with an intravascular (IV) injection of diazepam (0.5 mg/kg) and ketamine (8 mg/kg). After being properly sedated, the animals were weighed, placed on an operating table, and monitored with pulse oximetry and electrocardiography. Under Ultrasonography-guided, a jugular venous line was inserted and a 4 mg/kg bolus of propofol was administered in order to facilitate intubation using a cuffed endotracheal tube with 8 mm internal diameter. After intubation, a gastric tube was inserted with the aim of preventing ruminal tympany which would result in increased intraabdominal pressure, and hence raise some ventilation problems and regurgitation.[8] The carotid artery was cannulated for blood pressure measurements and arterial blood gas (ABG) sampling. Sedation was maintained with 12 mg/kg/h propofol

Figure 1. An image of the ASC-1 ventilator with a description of its settings.

and 4 mcg/kg/h ketamine infusions[9] and 0.15 mg/kg rocuronium boluses were administered IV; therefore, the dependence on the ventilators was facilitated and asynchronous breathing was prevented.

Study Protocol

The sheep were randomly allocated for the mechanical ventilation either with a standard ICU ventilator (Maquet Servo S, Getinge, Sweeden) or with a ventilation using a new simple compression ventilator integrated with a manual BVM, namely the ASC-1, or to ventilation using the ASC-1 ventilator following a moderate lung injury established by a saline-lavage application. According to this allocation, the sheep were labeled as Sheep A, Sheep B and Sheep C, respectively. In order to standardize the positions of the sheep and to prevent any positional bias on the findings related with the ventilation, all three sheep were placed on their right sides after anesthesia and kept in this position throughout the study.

To establish a modified lung injury model in Sheep C, a saline-lavage technique was applied according to the literature.[10] Briefly, 1 liter of warm isotonic saline solution was instilled in 200 mL portions into the lungs within 1 hour and then removed by aspiration in order to prevent a sudden derangement of vitals. The resulting hypoxemia was assessed by an arterial partial pressure of O_2 (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (P/F) under 200 mmHg pressure. The lavage was repeated until this targeted hypoxemia (P/F between 100-200 mmHg) was obtained. The injury and ventilation status of the lungs were radiographically monitored by an X-ray device (Mobilett Mira Max Siemens, Erlangen, Germany) at the 30th minute after anesthesia and after the establishment of the lung injury.

To maintain the fluid-electrolyte balance and to supply all metabolic needs, 5% dextrose and Lactated Ringer infusions, and electrolyte replacements with the sodium bicarbonate, potassium chloride, and calcium gluconate or magnesium sulphate were applied, when needed.

At the 12th hour of the experiment, the study was ended by euthanizing the animals with a high dose xylazine and ketamine injection. The euthanized animals were dissected, and both lungs of the three sheep were surgically harvested for histological examinations.

Histological Evaluation

Both lungs were fixed in 10% neutral-buffered formalin solution. The pneumonectomy specimens were collected and processed at the Pathology Laboratory in the Faculty of Medicine of the Near East University. Approximately 3 mm-thick tissue samples were resected from each group, and twenty blocks were sampled from different regions of both lungs. The samples were routinely embedded in the paraffin blocks. These blocks containing the resected materials were serially sectioned at an average thickness of 3-4 µm and the sections were stained with hematoxylin-eosin and examined under a light microscopy. Two histologic slides (4 fields in each) were evaluated from each block. The following criteria were evaluated for histopathological evaluation: atelectatic changes, the presence of perivascular and peribronchial edema, the hyaline membranes and thrombi, the interstitial inflammatory infiltrate, the fibrosis and the necrosis.

Statistical Analysis

The sheep's vital signs and blood gas changes were monitored throughout the study in order to observe the effects of the novel BVM ventilator (ASC-1) and its reliability and safety for ventilation in a normal lung and an injured lung and these findings were compared with the findings from the conventional mechanical ventilator supported sheep. The injury and ventilation status of the lungs were radiographically displayed. The histological evaluation of the lungs focused on any detrimental effects of the new ventilator and the extent of any perivascular and peribronchial iatrogenic injury of the mechanical ventilation.

RESULTS

The chest X-rays of Sheep A and Sheep B are presented in Figure 2. Respiratory findings of lung injury were observed in Sheep B (Figure 2b) in comparison with Sheep A (Figure 2a). Both of the sheep's chest X-ray densities were increased.

Sheep A weighed 55 kg. Following anesthesia induction and endotracheal intubation, Sheep A was connected to a conventional ICU ventilator under a pressure-controlled ventilation mode in accordance with protective mechanical ventilation protocols (FiO_2 of 0.4, tidal volume of 6 mL per kg of predicted body weight, respiration rate of 15-20/min, PEEP of 6 cmH_2O, and inspiratory pressure of 20 cmH_2O at a target plateau lower than 30 cmH_2O). After a stabilization period of 40 minutes, the ABG showed a normal profile at pH: 7.43, pCO_2: 34 mmHg, pO_2: 350 mmHg, lactate concentration: 11 mg/dL, and base excess (BE):-1.7 with normal electrolyte levels. At the end of the study protocol, the euthanized Sheep A showed optimal ABG findings with only slight alterations in their ventilatory parameters according to the outcomes of the hourly follow-ups of gases. A histological analysis of the lungs revealed an interstitial infiltration of inflammatory cells in addition to diffuse lymphoid follicles and focal congestions in the alveolar walls of Sheep A (Figure 3).

Sheep B weighed 50 kg. Following the anesthesia induction and endotracheal intubation, Sheep B was connected to the ASC-1 ventilator with settings at 20 breaths/min, 6 lt/min of oxygen, 6 cmH_2O of PEEP under 26 cmH_2O inspiratory pressure, targeting an optimal blood gas change. After a stabilization period of 40 minutes, the ABG analysis revealed hypokalemia (2.8 mmol/lt K^+) and other electrolytes within the normal range (139 mmol/lt Na^+, 113 mmol/lt Cl^-, 1.24 mmol/lt ionized Ca^{+2}) at pH=7.48, pCO_2=24 mmHg, pO_2=92 mmHg, lactate=6 mg/dL and BE=-5.5 mEq/L. A bolus of 250 mL electrolyte solution mixed with

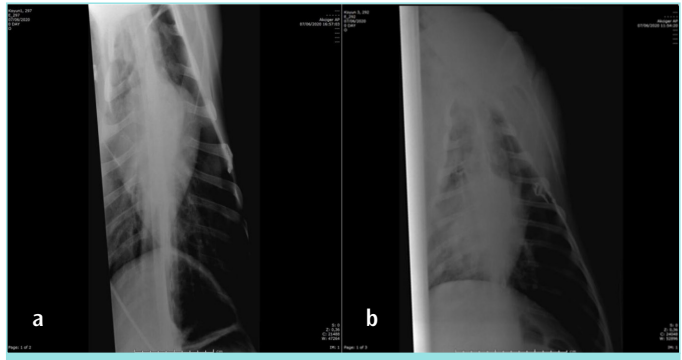

Figure 2. The chest X-rays of the lungs of the sheep under mechanical ventilation. The radiographies of the lungs were obtained after 30 minutes of ventilation with a conventional mechanical ventilator in Sheep A (a) and the novel ventilator (ASC-1) in Sheep B (b).

20 mmol/lt potassium was infused into Sheep B within 30 min, and the respiratory rate was shifted to 15/min and the inspiratory pressure to 24 cmH_2O under 10 lt/min of oxygen. Following these changes, the blood gases after 30 minutes of ventilation were measured at pH=7.27, pCO_2=54 mmHg, pO_2=360 mmHg, lactate=14 mg/dL, BE=-7.5 mEq/L, K^+=3.9 mmol/lt, Na^+=145 mmol/lt, and ionized Ca^{+2}=1.25 mmol/lt. Fluid infusion was sustained at a rate of 250 mL/hr. Then, the parameters were arranged according to the respiratory rate=24/min, oxygen=5 lt/min, inspiratory pressure=28 cmH_2O and PEEP=8 cmH_2O. After one hour, the blood gases were optimal at pH=7.38, pCO_2=46 mmHg, pO_2=208 mmHg, and lactate=12 mmol/lt. Thereafter, the ventilation was sustained with only slight alterations detected in the ventilation parameters at the 12th hour of the procedure in Sheep B. A histological evaluation of the lungs of Sheep B displayed a focal infiltration of inflammatory cells to the interstitial area and congestion of alveolar walls with a mild inflammatory cell infiltration together with patchy, scarce atelectatic and emphysematous foci (Figure 4).

Sheep C weighed 65 kg. Following anesthesia and endotracheal intubation, the animal was kept stable under vital monitoring with ventilation using an anesthesia machine (eternity AM852, Beijing, China). The baseline ventilation parameters were measured as FiO_2=0.5, PEEP=6 cmH_2O, tidal volume=400 mL/min and a respiration rate of 18/min (resulting in a dynamic compliance of 85 mL/cmH_2O and a resistance of 7 cmH_2O/ml/sec). ABG analysis showed pH=7.44, pCO_2=35.2 mmHg, pO_2=300 mmHg, lactate=13 mg/dL and BE=-2.1 mEq/L, with a resultant P/F ratio of 600 mmHg. The values at 1.5 hour from injury induction (described in the methods section) were as follows: FiO_2=0.5, PEEP=6 cmH_2O, tidal volume=380 mL/min, respiratory rate=14/min yielding a dynamic compliance of 31 mL/cmH_2O and a resistance of 18 cmH_2O/mL/sec. The gas exchange values were pH=7.29, pCO_2=47 mmHg, pO_2=85 mmHg, lactate=11 mg/dL and BE=-5 mEq/L. The resultant P/F ratio determined after the induction of the lung injury was 170. Therefore, Sheep C was transferred to the ASC-1 BVM compression ventilator and the parameters were set as 8 lt/min oxygen, a respiration rate of 16/min, PEEP at 10 cmH_2O and an inspiration pressure of 24 cmH_2O. Within 1 hour of ventilation by the ASC-1 ventilator, the ABG values were measured as pH=7.21, pCO_2=50 mmHg and pO_2=68 mmHg. Therefore, the fresh gas rate was increased to 12 lt/min, PEEP=12 cmH_2O, inspiration pressure to 30 cmH_2O, respiratory rate to 25/min, thus an optimal gas exchange was obtained at pH=7.21, pCO_2=56 mmHg and pO_2=86.5 mmHg. At the end of the 12 hour-period, the sheep was euthanized. The histological findings were focal interstitial inflammatory cell infiltration with alveolar congestion, the atelectatic and emphysematous fields observed in micrographs (Figure 5).

There were no differences between the histological findings of Sheep B and Sheep C with regards to the intensity of the inflammatory cell infiltration ratio, or the diffuseness of emphysema and atelectasis.

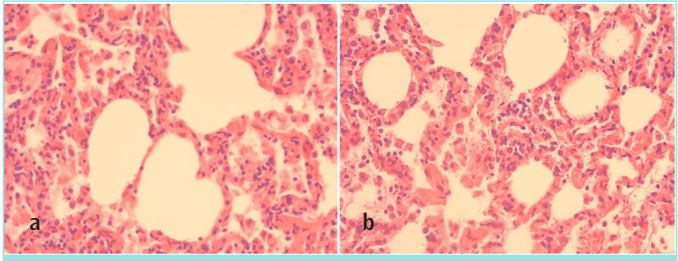

Figure 3. The histological micrographs of the specimens from the right lung (a) and the left lung (b) of Sheep A showing the intensive inflammatory cells (hematoxylin-eosin, x400).

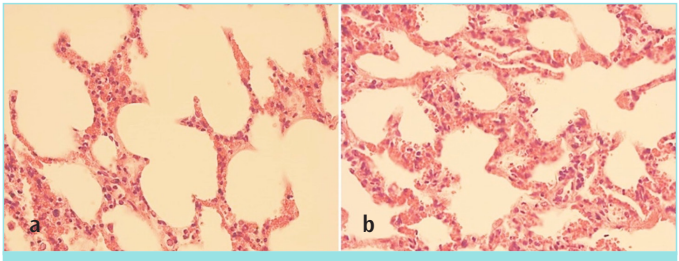

Figure 4. The histological micrographs of the specimens from the right lung (a) and the left lung (b) of Sheep B. (a) In the alveolar wall of the right lung, a vascular congestion and a few inflammatory cells were observed. (b) In the left lung, a vascular congestion and mild inflammatory infiltrates were observed in the emphysematous alveolar wall (hematoxylin-eosin, x400).

DISCUSSION

While BVMs are accredited as simple and useful medical devices which are very efficient in supporting the ventilation of patients with respiratory failure,[11] it is appreciated that even an automated BVM cannot replace a conventional ICU ventilator due to their clinical robustness. Mechanical ventilators are also reliable and safe devices which provide precise control over a large number of respiratory parameters; however, they are expensive and take considerable time to manufacture. In addition, in order to operate their system, qualified expertise is also needed. On the other hand, BVM ventilators can monitor a limited number of breathing parameters, and although they are less reliable, they are more cost-effective, easier to operate and even in low resource conditions, their production can be achieved in a short time. In the present experimental study, we evaluated the efficacy, safety and reliability of a novel BVM ventilator (ASC-1) developed for mechanical ventilation in an induced lung injury model and compared normal physiologic lung conditions with altered pathologic lung conditions in sheep. As expected, stabilizing the respiratory parameters of Sheep A was uncomplicated with an ICU ventilator, and stabilizing those of Sheep B and Sheep C's conditions was also achieved successfully with an ASC-1 ventilator, at least clinically.

The indications for using a BVM are hypercapnic respiratory failure, hypoxic respiratory failure, apnea, an altered mental status with

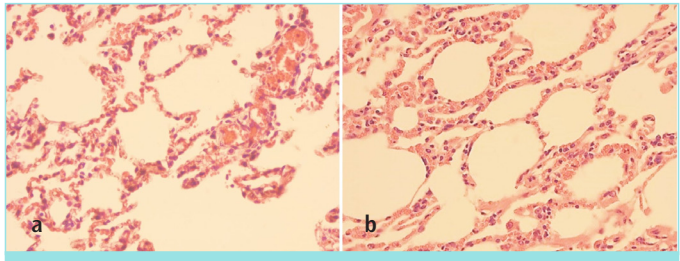

Figure 5. The histological micrographs of the specimens from the right lung (a) and the left lung (b) of Sheep C. (a) In the alveolar wall of the right lung, a vascular congestion and a few inflammatory cells were observed. (b) In the left lung, a vascular congestion and mild inflammatory infiltrates were observed in the emphysematous alveolar wall (hematoxylin-eosin, x400).

the inability to protect the airway, as well as for those patients who are undergoing anesthesia for elective surgical procedures. The contraindications are total upper airway obstruction and an increased risk of aspiration after paralysis and induction.[12] In the present animal model, a lung injury was induced in the lungs of a sheep in order to mimic a respiratory failure in a human. BVM ventilation can be aided by the use of a PEEP valve attached and titrated from 5 to 15 cmH_2O in order to improve oxygenation prior to intubation in patients who are unable to be appropriately pre-oxygenated with standard therapy. Therefore, we kept a PEEP of 6 cmH_2O on the ASC-1 as this pressure can open the lower esophageal sphincter and cause gastric insufflation and vomiting.[12]

Poor manual ventilation performance may depend on failures in delivering the quality of ventilation and a misunderstanding of the patient specific requirements. Unsafe manual ventilation may be alleviated by training reinforcement or accessory safety devices.[13,14] The ventilator used in this study, the ASC-1, is a simple mechanical ventilator into which a manual BVM can be incorporated. The appropriate ventilation may be indicated by electronic vital sign monitoring, the patient's chest rise, their skin color,[13] resistance on bag squeeze according to the patient lung pathology, CO_2 monitoring, and a flashing light on the BVM for rate of breath delivery.[15] Therefore, we compared the histopathological changes in the lung tissue samples of three sheep in order to determine the safety and reliability of the ASC-1 ventilator. The histologic examination of these samples showed a vascular congestion and emphysematous pattern in Sheep B and C's lungs; probably due to the higher driving pressures needed for ventilation with the ASC-1 ventilator. This suggests that even a sheep with an injured lung may be oxygenated by using this device. However, more advanced *in vivo* studies with larger samples are needed to understand how to use this device for the safe and protective ventilation of the lungs.

Study Limitations

Although there are several limitations to the present study including its very small number of experimental animals, this pilot study may facilitate the understanding that these types of simple ventilators can be easy-to-use and safe for ventilation. Even if mechanical ventilators are available, BVM devices may be readily used in emergency rooms and ambulances, as well as in clinics in low/middle-income countries where these devices may be the only option for the patients and clinicians until a mechanical ventilator is available.

CONCLUSION

It may be concluded that these ventilators, including the ASC-1, can be used for a limited period of time for the ventilation of patients with respiratory failure, particularly for the triage of patients where limited resources are available in terms of caregivers and devices, especially in pandemic-like conditions. We are aware of the small number of subjects in this study but this was an experimental pilot study which we consider may be a pioneer for more advanced studies on the exact safety and efficacy of ASC-1 ventilators in critical respiratory care.

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MAIN POINTS

- The recent global COVID-19 pandemic revealed how desperate conditions can result in great pressure due to uncountable patients being in need of mechanical respiratory support in times of shortages of resources or the unavailability of these devices. We now know that an adequate number of affordable, easy-to-use, safe and efficient ventilators are urgently needed in critical respiratory care settings.
- Bag-valve-mask (BVM) compression ventilators can be an alternative in such conditions, since they are low-cost and simple. In the present experimental study, we evaluated the efficacy, safety and reliability of a novel BVM ventilator (the ASC-1), which was developed for mechanical ventilation, in an induced lung injury model and compared the normal physiologic lung conditions with pathologically altered lung conditions in sheep.
- The injury and ventilation status of the lungs of the sheep were examined radiographically and biopsies collected from the lungs were examined histologically. Resulting in no further injury, it may be concluded that BVM compression ventilators can be used for a limited period of time for the ventilation of patients with respiratory failure, particularly for the triage of patients where limited resources are available in terms of caregivers and devices, especially in pandemic-like conditions.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Committee of the Near East University for the Animal Care and Use (approval number: 2020/116, date: 20.05.2020).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H.G., G.E., Ç.G., Concept: A.H.G., T.Ö., Design: T.Ö., G.E., Ö.T., G.M., Data Collection and/or Processing: A.H.G., Ç.G., H.Ö., Ö.T., G.M., Analysis and/or Interpretation: A.H.G., G.E., Ç.G., Ö.T., G.M., Literature Search: A.H.G., G.E., Writing: A.H.G., T.Ö., G.E., H.Ö.

DISCLOSURES

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

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

REFERENCES

1. Goligher E, Ferguson ND. Mechanical ventilation: epidemiological insights into current practices. Curr Opin Crit Care. 2009; 15(1): 44-51.
2. Kirton O. Mechanical Ventilation in the Intensive Care Unit. 2011. The American Association for the Surgery of Trauma. Available from: https://www.aast.org/resources-detail/mechanical-ventilation-in-intensive-care-unit
3. Dar M, Swamy L, Gavin D, Theodore A. Mechanical-Ventilation Supply and Options for the COVID-19 Pandemic. Leveraging All Available Resources for a Limited Resource in a Crisis. Ann Am Thorac Soc. 2021; 18(3): 408-16.

4. Halpern P, Dang T, Epstein Y, Van Stijn-Bringas Dimitriades D, Koenig KL. Six hours of manual ventilation with a bag-valve-mask device is feasible and clinically consistent. Crit Care Med. 2019; 47(3): e222-6.

5. Dafilou B, Schwester D, Ruhl N, Marques-Baptista A. it's in the bag: tidal volumes in adult and pediatric bag valve masks. West J Emerg Med. 2020; 21(3): 722-6.

6. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med. 2004; 32(9 Suppl): S345-51.

7. Paladino L, Silverberg M, Charchaflieh JG, Eason JK, Wright BJ, Palamidessi N, et al. Increasing ventilator surge capacity in disasters: ventilation of four adult-human-sized sheep on a single ventilator with a modified circuit. Resuscitation. 2008; 77(1): 121-6.

8. Lin H. Preanesthetic considerations. In: Farm animal anesthesia: cattle, small ruminants, camelids, and pigs. Lin H, Walz P, editors. John Wiley & Sons. UK; 2014.p.1-16.

9. Dzikiti BT, Stegmann FG, Dzikiti LN, Hellebrekers LJ. Total intravenous anaesthesia (TIVA) with propofol-fentanyl and propofol-midazolam combinations in spontaneously-breathing goats. Vet Anaesth Analg. 2010; 37(6): 519-25.

10. Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2008; 295(3): L379-99.

11. Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010; 122(18 Suppl 3): S729-67. Erratum in: Circulation. 2011; 123(6): e236. Erratum in: Circulation. 2013; 128(25): e480.

12. Bucher JT, Vashisht R, Ladd M, Cooper JS. Bag Mask Ventilation. [Updated: 2021 Apr 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441924/

13. Mumma JM, Durso FT, Dyes M, Dela Cruz R, Fox VP, Hoey M. Bag Valve Mask Ventilation as a Perceptual-Cognitive Skill. Hum Factors. 2018; 60(2): 212-21.

14. Khoury A, Sall FS, De Luca A, Pugin A, Pili-Floury S, Pazart L, et al. Evaluation of Bag-Valve-Mask Ventilation in Manikin Studies: What Are the Current Limitations? Biomed Res Int. 2016; 2016: 4521767.

15. Culbreth RE, Gardenhire DS. Manual bag valve mask ventilation performance among respiratory therapists. Heart Lung. 2021; 50(3): 471-5.

RESEARCH ARTICLE

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Developing a Scale to Make Suggestions to Overweight People for Efficient Weight Loss and Weight Management

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Abstract

BACKGROUND/AIMS: To develop a scale to assess potentially adequate suggestions which can be made to overweight individuals to aid in their weight loss.

MATERIALS and METHODS: In this cross-sectional study, a scale of 28 items was initially prepared from a pool of potential items. Using the Davis technique and content validity index assessment, a scale of 14 items was prepared. A 3-Likert type scaling method was used for response assessment. A total of 77 overweight individuals were recruited to participate in this survey two times within an interval of three weeks. To assess the reliability of the scale, the test/re-test technique and Cronbach's alpha parameter were employed. IBM SPSS version 22.0 was used for statistical analysis. For all tests, the confidence interval and p-value were set at 95% and ≤0.05, respectively.

RESULTS: The content validity index for the 14 items was 80% or higher. The reliability correlation coefficient for the scale, using the test/re-test method, was 0.763 (p=0.001). The overall Cronbach's alpha score was 0.737, which did not decrease after eliminating any of the items. The Kaiser-Meyer-Olkin measure was calculated to be 0.631, which was acceptable. The VARIMAX rotated factor analysis yielded five factors with 64.33 percent of the variance. On loading the 14 items on these five factors, the item loading values ranged from 0.505 to 0.849.

CONCLUSION: The 14-item scale showed good validity and fairly acceptable reliability. It can be used to provide adequate and useful suggestions to overweight individuals in order to aid in their weight loss program.

Keywords: Overweight, obesity, nutritionists, weight reduction programs, cross-sectional study

INTRODUCTION

Obesity is defined as the excessive or abnormal accumulation of fat in the body which poses a health risk. According to recent World Health Organization guidelines, an individual with a body mass index (BMI) more than or equal to 25 kg/m^2 is considered to be overweight, and those with BMI more than or equal to 30 kg/m^2 are considered to be obese.[1] During the past few decades, with increases in the consumption of processed food and sedentary lifestyles, the prevalence of obesity has markedly increased. Several studies have shown that obesity adversely affects the health of individuals.[2] It leads to several physiological problems and physical disabilities. It also increases the risk of several non-communicable diseases, such as cancer, diabetes, cardiovascular disorders, hypertension, depression, metabolic syndromes, neurological illness, etc.[1,2] Several studies have also demonstrated that obesity is associated with higher rates of admission to hospitals and intensive care units.[3] Recent studies have also shown that high BMI is directly associated with worse outcomes among coronavirus disease-2019 (COVID-19) patients.[3,4] It has previously been reported that even a 10% reduction in the weight of individuals with severe obesity can lead to

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significant improvements. However, in most cases, even after various pharmacological and surgical interventions, such as bariatric surgery, overweight individuals seem to revert back to their previous obese conditions.[5,6]

The rise in healthcare expenses has brought about a dire need to employ and adopt preventive management strategies in order to facilitate early disease prevention, especially in the current era of novel disease variants and bio-terrorism.[7] By definition, preventive medicine refers to the implementation of strategies to prevent any serious health problems in the future via the early detection and prevention of adverse health conditions. Such a management approach is essentially the most cost-effective way to reduce the risk of more critical comorbidities.[7] Preventive medicine is the most basic feature of primary health care services. While implementing prevention techniques for obesity, family practitioners play a critical role.

It is noteworthy that psychological and behavioral instincts majorly impact the eating habits of an individual. These factors also influence the outcomes of weight loss strategies. Several researchers have previously used self-reported measures in order to assess the potential behavioral predictors among obese individuals.[8]

Current eating habits and environmental changes have collectively affected the overall physical, physiological, and psychological well-being of people worldwide. With this in mind, we hypothesized that developing a scale involving both the internal factors of patients, such as their eating habits, and the external factors, such as expert support and environmental influences, would help health care providers and overweight individuals to focus on the efficient management of their weight loss programs. This study aimed to develop a 14-item scale in three different domains in order to assess the potential markers and suggestions which can help in weight reduction and long-term weight management.

MATERIALS AND METHODS

Questionnaire

Ethical approval for this study was obtained from the Ethics Committee of Private Hürrem Sultan Hospital (approval number: 2020-39, date: 13.11.2020). Initially, we prepared a "pool of items" which overweight people must do in their daily life to lose weight. Then, we prepared a scale of 28 items from this pool. The items were divided into three major domains: namely "*Requiring expert support*" (expert support), "*Regulation of habits*" (habits), and "*Regulation of environmental factors*" (environment). The *expert support*, *habits*, and *environment* sections contained seven, thirteen, and eight items, respectively. This scale was then sent to five dieticians. Then, the Davis technique was applied and, based on the suggestions of dieticians and authors, 14 items were determined to be unsuitable and were removed from the scale.

From the domain of *expert support*, one item was removed:

"*I expect my psychologist to solve my problem about weight*"

From the domain of *habits*, seven items were removed:

"*It is necessary to do sports every day*", "*It is necessary to not eat at night*", "*You should not eat too much bread*", "*Meals should not be skipped*", "*You should not eat in times of sadness or trouble*", "*You need to spend as little time as possible in front of the TV/computer*", and "*It is necessary to have snacks*".

From the domain of *environment*, seven items was removed:

"*There should be less variety in the house*", "*It is necessary to follow the advice of people who have lost weight*", "*You should not drink alcohol*", "*You should not accept invitations*", "*You should not accept treats*", "*It is useful to see before/after pictures of people who have lost weight*".

The remaining items were as follows:

Expert support domain:

1. Dietician's advice should be followed,

2. I expect my dietician to motivate me,

3. The doctor's advice should be followed,

4. I expect my doctor to motivate me,

5. The psychologist's advice should be followed,

6. I must learn correct nutrition,

Habits domain:

7. Serving plates should be small,

8. A role model is needed to be motivated,

9. Eating too quickly is bad,

10. The mouthfuls of food must be small,

11. One should restrain from eating junk food,

12. One should restrain from too much sweet food,

Environment domain:

13. One shouldn't eat with people who have large appetites,

14. No other activities should be done while eating.

The content validity index for items 1-10 and 14 was 100% and for items 11-13, it was 80%.

Study Participants

Initially, we recruited 14 individuals to participate in a trial survey in order to obtain feedback regarding whether it was difficult to understand any item. Once all the individuals confirmed that they did not experience any difficulty, a total of 77 individuals were enrolled into this study. The sample size was determined after multiplying the number of questions by 5.

Number of questions was 14 and so;

14x5=70 participants

Following this, taking into account people dropping out, an extra 10% of the number of participants was added.

70 + (10% of 70)=77 total participants.

Inclusion Criteria

The inclusion criteria of the participants included being aged between 18 and 65 years, having a BMI more than or equal to 25 kg/m^2, including obese individuals, and the ability to participate in both of the surveys conducted 3 weeks apart.

Exclusion Criteria

The exclusion criteria included not able to participate in both of the surveys "on time", being aged less than 18 years or more than 65 years, having a BMI less than 25 kg/m^2 or suffering from a cognitive defect which impaired the ability to understand the scale and fill the questionnaire. All the participants provided informed consent.

Survey

The participants were asked to undertake the survey twice at an interval of three weeks. The average time for completion of the survey was 3 minutes. In order to ensure the validity of the survey, we obtained the opinions of five dieticians, we employed a content validity method, and a translation validity method. Additionally, in order to ensure the reliability of our results, we employed the method of repeating the form.

Scale response: In survey studies, several types of response assessment tools are used, such as 5- or 7-Likert scaling. However, such large assessment tools exhibit lower performance than smaller tools, such as 3-Likert scaling.[9] Thus, in this study, we used the 3-Likert type scale to assess the responses as shown below:

1 point - *No* or *not at all*

2 points - *Partly* or *sometimes*

3 points - *Yes* or *always*

Statistical Analysis

The recorded data was compiled and analyzed using Microsoft Excel 2010 and IBM SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA). We used Cronbach's alpha and test-retest reliability analysis to evaluate the reliability of our scale. Factor extraction was conducted using principal component analysis. For all tests, the confidence interval and p-value were set at 95% and ≤0.05, respectively.

The purpose of the scale developed was to assess the understanding of obese people regarding weight loss and thereby provide appropriate suggestions and motivation for them. A 3-Likert scale was used for the assessment where points were assigned to the responses as follows:

- *No* or *not at all* = 1 point

- *Partly* or *sometimes* = 2 points

- *Yes* or *always* = 3 points

A cut-off point was not set in the current study. It was avoided in order to eliminate the polarization of responses and thus a loss of information.[10] Rather, the responses were analyzed over the complete range of the scale.

RESULTS

Reliability Assessment

Reliability analysis showed that the inter-item correlation coefficients ranged from -0.11 to 0.553. Item-total correlation coefficients ranged between 0.152 and 0.484. The Cronbach's alpha coefficient was 0.737, which did not increase when deleting any items (Table 1).

Furthermore, the test-retest reliability assessment revealed a correlation coefficient of 0.763 (p=0.001) which was acceptable (Table 2).

Factor Analysis

The ratio of observations to variables was approximately equal to 5.5:1 in the present study (sample size = 77, number of items = 14). The minimum acceptable ratio according to Hair et al.[11] is 5:1. Thus,

Table 1. Reliability analysis

Questionnaire items	Corrected item total correlation coefficients	Alpha if item deleted	Cronbach's alpha
Requiring expert support			
The dietician's advice should be followed	0.454	0.708	
I expect my dietician to motivate me	0.484	0.705	
The doctor's advice should be followed	0.385	0.717	
I expect my doctor to motivate me	0.352	0.719	
The psychologist's advice should be followed	0.379	0.716	
I must learn correct nutrition	0.484	0.711	
The regulation of habits			
Serving plates should be small	0.331	0.721	**0.737**
A role model is needed to be motivated	0.283	0.729	
Eating too quickly is bad	0.152	0.737	
Mouthfuls must be small	0.328	0.722	
One should restrain from eating junk food	0.187	0.737	
One should restrain from eating too much sweet food	0.201	0.733	
The regulation of environment			
One shouldn't eat with people who have strong appetites	0.435	0.709	
No other activities should be done while eating	0.433	0.709	

the ratio of observations to variables in our study satisfies the above criteria. Also, the data matrix should have sufficient correlations to justify the application of factor analysis techniques. An examination of the correlation matrix did not reveal any values equal to or above 0.90, which indicates that the data does not have any major collinearity issues. The Bartlett's test is significant at a level of 0.001 which suggests the overall significance of the correlation matrix. Another measure which checks for the appropriateness of the factor analysis is the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy. The value for KMO in the present study was equal to 0.631, which falls in the acceptable range (above; 0.50). Principal Component analysis which considers the total variance was used to extract the factors. The latent root criterion of retaining factors with eigenvalues equal to or greater than 1 in combination with the screen test (Figure 1) was employed in order to determine the number of factors to be retained for interpretation. In order to improve the interpretation, orthogonal (VARIMAX) rotation was applied to the factor matrix. Before extracting the factors, the factor-loading matrices and the communalities were examined in order to evaluate the different items for possible deletion. The items with factor loadings below ±0.4, substantial cross-loadings or communalities less than 0.40 were considered for deletion. Based on this, none of the items needed to be deleted. The VARIMAX rotated factor analysis of the set of 14 items as shown in Table 3 yielded five factors which accounted for 64.33 percent of the variance. All 14 items were loaded on these 5 factors. The item loadings ranged from 0.505 to 0.849 (Table 3).

DISCUSSION

Obesity is a direct reflection of changing and irregular eating behaviors perceived from social, environmental and emotional factors.[12] Psychological factors also play a critical role in weight gain in an individual. These are essentially the most important factors in determining the outcome of weight loss measures.[8] Emotional eating behavior arises due to negative emotions such as sadness and anger as a result of poor physiological outcomes. Mindless food intake has been associated with higher anxiety and stress levels.[12] Previously, several self-reported measures have been developed to elucidate the association of obese individuals with food, such as their age of onset of obesity, their weight cycling history, the power of food scale, the modified Yale Food Addiction Scale, the Barratt Impulsiveness Scale, the three-factor eating questionnaire, etc. Also, there have been studies on the prevalence of obesity in corporate organizations considering five major risk factors, namely, *unhealthy diet*, *physical inactivity*, *stress*, *alcohol consumption* and *smoking*. Out of these five risk factors, only two, *unhealthy diet* and *physical inactivity*, were found to have significant relationships (p<5%) with being overweight and obesity.[13]

Different scales focus on different parameters for the assessment and management of obesity. Here, we focused on three major domains, namely, *expert support*, *habits*, and *environment*. The eating behavior of an individual has been demonstrated to be a complex process which is affected by both internal (internal homeostasis) as well as external (social and environmental influences) factors.[14] The energy homeostasis of our body aims to equate the energy intake with its overall needs. However, due to the influence of external factors, such as palatability and availability, the net food intake might be higher than is needed, which leads to excess energy intake.[15]

The development of any new scale incorporates the verification of its validity and reliability. The validity of any new scale is evaluated via its validity/correlation coefficient. The value of this coefficient varies between +1.0 and -1.0 and is directly associated with the validity of the scale.[9] The validity of any scale comprises of internal validity, which represents the actual meaning of the items, and external validity, which indicates the generalizability potential of the scale. Here, we used the content validity method, which is a type of translation validity method. In order to achieve this, we applied the Davis technique in order to validate the content of our scale. In this technique, each item was given a grade of 1 to 4 by each dietician, where the grades of 1, 2, 3, and 4 referred to "*item appropriate*", "*item should be reviewed slightly*", "*item should be reviewed seriously*", and "*item not appropriate*", respectively. The first two grades were considered as positive and the last two as negative. For each item, the content validity index was calculated as follows:

Content validity index = (the number of positive grades achieved/the total number of experts)*100

Those items with a content validity index of more than or equal to 80% were included in the survey and rest were omitted.[16] Based on this calculation, 14 items were determined to be valid and were included in the scale.

Furthermore, the reliability of a scale essentially refers to the consistency in the results even after repetition. In this context, the time elapsed between repetitions plays an important role. For instance, if the time between the two assessments is too short, it leads to an inaccurate increase in the reliability because of the recall of the previous answers given by the participants. On the other hand, if the time elapsed is too long, it often leads to changes in the measurement parameters or conditions, which leads to a decrease in reliability. In addition, another

Table 2. Assessment of test-retest reliability by correlation of pre-test and post-test scores

	Post-test	
	Correlation coefficient	p-value
Pre-test	0.763	0.001*

Test applied: Pearson's correlation test, *indicates statistically significant correlation.

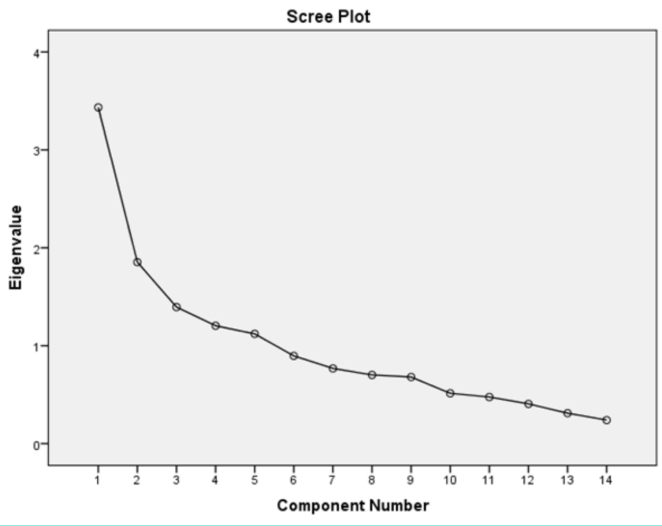

Figure 1. Scree plot.

Table 3. Distribution of items according to components

Item	Component				
	1	2	3	4	5
1. I expect my doctor to motivate me	0.700				
2. I expect my dietician to motivate me	0.803				
3. The doctor's advice should be followed	0.681				
4. The psychologist's advice should be followed	0.583				
5. The dietician's advice should be followed	0.716				
6. I must learn correct nutrition	0.505				
7. A role model is needed to be motivated		0.615			
8. One should restrain from eating too much sweet food				0.849	
9. One should restrain from eating junk food					0.789
10. Eating too quickly is bad				0.618	
11. Mouthfuls must be small			0.833		
12. No other activities should be done while eating			0.805		
13. One shouldn't eat with people who have large appetites		0.789			
14. Serving plates should be small		0.728			

Items included in: 1st Component: Q.1 to Q.6, 2nd Component: Q.7, Q.13, Q.14, 3rd Component: Q.11, Q.12, 4th Component; Q.8 and Q.10, 5th Component: Q.9.

parameter, known as agreement/compliance, also facilitates in the assessment of the reliability of a scale. In this parameter, multiple observers conduct the same analyses. The higher the number of similar observation results and observers is, the higher is the reliability of the scale is. Ideally, all the items of a scale must contribute to enhance the reliability of the scale. It is noteworthy that high reliability does not imply high validity, but a tool with high validity also has a high reliability.[17] Here, we employed the form repetition method, also known as the test-retest method (invariance over time) in order to verify the reliability of our scale. We surveyed the same population of participants using the same scale with an interval of 2-4 weeks.[9] Then, the measured values obtained from the surveys were correlated and the values of the correlation coefficients were determined. The value of these correlation coefficient varies from -1.0 to +1.0. The higher the value of the coefficient, the higher the correlation between the measured values is, which indicates good reliability. For a scale to show good reliability, the value of the reliability correlation coefficient must be at least 70%.[17] Our results showed an overall correlation coefficient of 0.763 (p=0.001) among the measured values of the two surveys, which indicated acceptable reliability (Table 2). In addition, we observed that the item-wise Cronbach's alpha scores varied from 0.705 for item 2 (*I expect my dietician to motivate me*) to 0.737 for items 9 (*Eating too quick is bad*) and 11 (*One should restrain from eating junk food*). Overall, the Cronbach's alpha score of the scale was 0.737, which indicated fairly good reliability. The deletion of any of the 14 items did not increase the Cronbach's alpha score and reliability of the scale. The corrected-to-total item correlations were generally strong, which indicated that the items on the same factor represented a common concept or construct and the adoption of the aggregate score, as a proxy for the common factor.

Several factors contribute to the incidence of obesity. It is necessary to implement preventive measures at an early stage. Medical practitioners and dieticians play a crucial role in this regard. To the best of our knowledge, this is the first study which incorporates both expert support and eating habits domains within the same scale. In a recent review, Mastrocola et al.[18] (2020) demonstrated that training programs conducted around the world for medical students and residents are insufficient in providing adequate obesity education. They suggested that medical schools should work on the inclusion of obesity education programs in their curricula. For optimal obesity management, it is necessary to provide appropriate education and training to graduate and undergraduate medical students.[18]

Considering the domain of *expert support*, constant assistance from the dietician or doctor and a focus on good mental health to attain a good psychological balance might help patients to adhere to weight loss interventions and motivate them for continued weight management. A study by Dicker et al.[19] found that motivation at 4 weeks could decide the further adherence towards self-management and so help the individual to adhere to a target of a further 16 weeks of weight loss. Empathy is used in motivational interviewing, which has been suggested to enhance weight loss outcomes. Hence, incorporating different aspects of social behaviors such as empathy, can expedite weight loss outcomes. Additionally, motivational nutrition programs and training for patients can be employed to assess their nutritional literacy in a form of cognitive-behavioral approach and to improve their health through weight reduction, lower cardiovascular risk and other physiological functions.[20] Reforming eating habits also leads to improvements in physiological balance. This significantly improves sticking to eating timetables and also regulates the circadian rhythm. It also leads to a reduction of oxidative stress and preserves hormonal balance. An observational study on nutritional psychiatry investigated the role of individual dietary factors and overall dietary patterns regarding reductions in depression, anxiety, and sleep disorders.[21] Engaging in social activities also discourages individuals from unhealthy diets and also influences others in terms of healthy eating and regular physical activity. This leads to better weight management.[22] There were a few limitations of this study. We did not classify the participants on the basis of their age, gender, sociodemographic characteristics, or occupation. Sociodemographic characteristics and occupations directly or indirectly affect the psychological state of an individual. As stated earlier, the eating behavior of an individual is significantly affected by their psychological well-being. Furthermore, when faced with the same

problems, males and females often react and compensate differently, which also contributes to their habits of excess eating. Some previous studies have shown that individuals who encounter obesity at an early age face a much larger problem in tackling this condition and often revert back to an obese condition at a later stage in life. Simmonds et al.[23] reported that individuals who developed obesity at an early age were about five times more likely to exhibit obesity during adulthood compared to those who did not. Furthermore, we observed that the scale showed only fairly acceptable reliability. We propose the use of this scale with a larger study sample in order to further elucidate its degree of reliability.[23] In a clinical set-up, this scale can be used to assess the awareness and receptiveness of obese people to various facts and suggestion regarding their weight loss. Based on their responses, an effective weight loss program can be customized. Additionally, during a weight loss program, the survey can be re-taken in order to check whether the individual requires more assistance and suggestions, which were not required at the beginning. For public health, this survey can be used to assess the understanding of the general public regarding their awareness regarding weight loss and weight management and thereby provide appropriate suggestions for them.

CONCLUSION

Here, we developed a novel scale to determine potentially useful suggestions which can be given to overweight individuals in order to aid in their weight loss. The items in this scale were validated using the content validity method and Davis technique, which led to the formation of a 14-item scale. The reliability of this scale was assessed using the test-retest method, which revealed an acceptable reliability correlation coefficient. The Cronbach's alpha score and corrected-to-total item correlation scores also indicated fairly good reliability.

MAIN POINTS

- Our goal was to develop a scale to assess potentially appropriate suggestions which can be offered to overweight individuals in order to aid in their weight loss.
- In this cross-sectional study, a scale of 28 items was initially prepared from a pool of potential items.
- A total of 77 overweight individuals were recruited to participate in this survey two times within an interval of three weeks.
- The 14-item scale showed good validity and fairly acceptable reliability and so can be used to provide adequate and useful suggestions to overweight individuals to aid in their weight loss program.

ETHICS

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of Private Hürrem Sultan Hospital (approval number: 2020-39, date: 13.11.2020).

Informed Consent: All the participants provided informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ü.D., A.M., Concept: Ü.D., Design: Ü.D., Data Collection and/or Processing: Ü.D., A.K., Analysis and/or Interpretation: Ü.D., A.M., Writing: Ü.D., A.M., A.K.

DISCLOSURES

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

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REFERENCES

1. de Siqueira JVV, Almeida LG, Zica BO, Brum IB, Barceló A, de Siqueira Galil AG. Impact of obesity on hospitalizations and mortality, due to COVID-19: A systematic review. Obes Res Clin Pract. 2020; 14(5): 398-403.
2. Donofry SD, Stillman CM, Erickson KI. A review of the relationship between eating behavior, obesity and functional brain network organization. Soc Cogn Affect Neurosci. 2020; 15(10): 1157-81.
3. Muscogiuri G, Pugliese G, Barrea L, Savastano S, Colao A. Commentary: Obesity: The "Achilles heel" for COVID-19? Metabolism. 2020; 108: 154251.
4. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020; 28(7): 1195-9. Erratum in: Obesity (Silver Spring). 2020; 28(10): 1994.
5. Rakel RE, Rakel DP. Texbook of Family Medicine. Obesity (36. chapter). 9th Edition. Elsevier, Inc. 2016.
6. Ferri FF. Ferri's Clinical Advisor. Elsevier, Inc. Philadelphia: Printed in the USA; 2016.p.882-85.
7. Razzak MI, Imran M, Xu G. Big data analytics for preventive medicine. Neural Comp Appl. 2020; 32: 4417-51.
8. Akter S, Dawson JA, Kahathuduwa CN, Chin SH, Binks M. Psychological and weight history variables as predictors of short-term weight and body fat mass loss. Obes Sci Pract. 2019; 6(2): 152-61.
9. Aydemir O, Eren I, Savaş H, Kalkan Oğuzhanoğlu N, Koçal N, Devrimci Ozgüven H, et al. Development of a questionnaire to assess inter-episode functioning in bipolar disorder: Bipolar Disorder Functioning Questionnaire. Turk Psikiyatri Derg. 2007; 18(4): 344-52.
10. Westland JC. Information loss and bias in likert survey responses. PLoS ONE. 2022; 17(7): e0271949.
11. Hair JF, Sarstedt M, Hopkins L, Kuppelwieser VG. Partial Least Squares Structural Equation Modeling (PLS-SEM): An Emerging Tool in Business Research. European Business Review. 2014; 26: 106-21.
12. McAtamney K, Mantzios M, Egan H, Wallis DJ. Emotional eating during COVID-19 in the United Kingdom: Exploring the roles of alexithymia and emotion dysregulation. Appetite. 2021; 161: 105120.
13. Gupta H, Garg S. Obesity and overweight—their impact on individual and corporate health. Journal of Public Health. 2020; 28(2): 211-8.
14. Cappelleri JC, Bushmakin AG, Gerber RA, Leidy NK, Sexton CC, Karlsson J, et al. Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. Int J Obes (Lond). 2009; 33(8): 913-22.
15. Yeomans MR, Blundell JE, Leshem M. Palatability: response to nutritional need or need-free stimulation of appetite? Br J Nutr. 2004; 92(S1): S3-14.
16. Kocak C, Albayrak SA, Duman NB. Developing an attitude scale for nurses in caregiving roles: validity and reliability tests. J Edu Res Nurs. 2014; 11(3): 16-22.
17. Ercan I, Kan I. Reliability and Validity in the Scales. Uludag Universiy Journal of College of Medicine. 2004; 30: 211-6.

18. Mastrocola MR, Roque SS, Benning LV, Stanford FC. Obesity education in medical schools, residencies, and fellowships throughout the world: a systematic review. Int J Obes (Lond). 2020; 44(2): 269-79.

19. Dicker D, Alfadda AA, Coutinho W, Cuevas A, Halford JCG, Hughes CA, et al. Patient motivation to lose weight: Importance of healthcare professional support, goals and self-efficacy. Eur J Intern Med. 2021; 91: 10-6.

20. Di Onofrio V, Gallé F, Di Dio M, Belfiore P, Liguori G. Effects of nutrition motivational intervention in patients affected by type 2 diabetes mellitus: a longitudinal study in Naples, South Italy. BMC Public Health. 2018; 18(1): 1181.

21. Godos J, Currenti W, Angelino D, Mena P, Castellano S, Caraci F, et al. Diet and Mental Health: Review of the Recent Updates on Molecular Mechanisms. Antioxidants (Basel). 2020; 9(4): 346.

22. Varkevisser RDM, van Stralen MM, Kroeze W, Ket JCF, Steenhuis IHM. Determinants of weight loss maintenance: a systematic review. Obes Rev. 2019; 20(2): 171-211.

23. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev. 2016; 17(2): 95-107.

RESEARCH ARTICLE

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COVID-19 Associated Brain Fog and Neurocognitive Assessment

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Abstract

BACKGROUND/AIMS: In this study, we aimed to make detailed neurocognitive assessments of patients who presented with brain fog after coronavirus disease-2019 (COVID-19) infection and to investigate their complaints after one-year of follow-up.

MATERIALS AND METHODS: Patients who had COVID-19, which was not severe enough to require intensive care, and who subsequently applied to neurology due to cognitive complaints were included in this study. A neurocognitive test battery was applied to those patients who agreed to detailed examination (n=16). This battery consisted of the following tests: mini-mental test, enhanced cued recall test, phonemic fluency, categorical fluency, digit span, counting the months backwards, clock-drawing, arithmetic operations, trail-making, cube copying, intersecting pentagons, and the interpretation of proverbs and similes. At one year, the patients were called by phone and questioned as to whether their cognitive complaints had persisted. Those patients with ongoing complaints were invited to the hospital and re-evaluated via cognitive tests. The results are presented in comparison with age-matched healthy controls (n=15).

RESULTS: Almost all of the patients' scores were within the "*normal*" range. The *Spontaneous recall* of the patients was statistically significantly lower than the controls (p=0.03). Although there were decreases in executive functions and central processing speed (trail making-A, trail making-B and reciting the months backwards tests) in the patient group, these differences were not statistically significant (p=0.07; p=0.14 and p=0.22, respectively) compared to the controls. We observed that the cognitive complaints of the patients had disappeared by the one-year follow-up.

CONCLUSION: In our patients with brain fog, most of whom had mild COVID-19, we observed that among all cognitive functions, memory domain was most affected compared to the controls. At the one-year follow-up, COVID-related brain fog had disappeared.

Keywords: Long COVID, brain fog, executive functions, memory, mental processing speed

INTRODUCTION

Cognitive complaints are an important cause for referral to neurology outpatient clinics in people recovering from coronavirus disease-2019 (COVID-19).[1,2] The expression "*brain fog*" is generally used to describe mental slowing, confusion, interruptions in thought and attention. This phenomenon is frequently reported by patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection after the acute period, and is called "*post-COVID brain fog*". Although the pathophysiology of brain fog is not clearly known, it has been claimed that neurogenic inflammation may play a role in its background.[3] In some recent publications, it has been shown that there was an increase in protein in the cerebrospinal fluid of those patients with post-COVID brain fog even after months, and some findings pointing to inflammation were observed.[4] Whether these findings are indicative of an overstimulated systemic immune reaction or a consequence of an intrathecal immune response has not been discerned to date.

In terms of clinical features; it has been observed that some patients experience mental slowdown, confusion, an inability to focus, an inability to find words, and short-term memory and planning problems after

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the COVID-19 infection has passed.[5,6] It is known that these cognitive complaints can persist even months after patients have recovered from their signs of infection, and they are then considered to be part of a prolonged (long) COVID or post-COVID syndrome.[7,8] It has been reported that cognitive impairment is more prominent in individuals with severe disease.[6,9] It is a matter of debate whether COVID-19 will cause cognitive sequelae in the long term. However, it has already been seen that patients lose functionality in their work, school and other daily life activities. For many patients, these cognitive problems are a source of additional anxiety. It is important in many ways to define the mental problems which patients experience, to determine their details, and especially to know their prognosis. If this phenomenon is better understood, first of all, appropriate management of patients can be provided and it will be possible to distinguish COVID-related cognitive problems from other diseases. On the other hand, those patients who need follow-up will be identified and unnecessary medical applications will be prevented for others.

Cognitive impairment associated with SARS-CoV-2 infection has been reported in many studies and reviews.[1,2,5-14] In some of these publications, an objective neuropsychological criterion revealing cognitive impairment was lacking, while in others, general cognitive screening tests such as the mini-mental test (MMSE) and the montreal cognitive assessment (MoCA) were used. Although there are a couple of large field studies pointing to cognitive dysfunction or memory issues after COVID-19, studies which report detailed neurocognitive testing and that also present objective data are relatively few.[14] Impairments in attention, executive functions, and short-term memory are evident in test-based examinations.[6,12,14] It is noteworthy that mental arithmetic, abstract thinking, language and visuospatial skills are less commonly evaluated. However, in our daily practice, it is observed that a substantial number of patients complain of not being able to calculate or of having difficulty in speaking. The combination of clinically heterogeneous, i.e. mild, severe and critical COVID-19 cases, in these study groups constitutes an important limitation in the literature to date.

In this study, we aimed to make a complete neurocognitive evaluation, instead of focusing on certain cognitive areas, in those patients who had COVID-19 which was not severe enough to require intensive care and who then applied to neurology due to cognitive complaints. For this purpose, we arranged one-to-one interviews with these patients and applied standard tests which have been frequently used and validated for our society. These test results are presented in comparison with age-matched healthy controls. After one year, all patients were interviewed on the phone, their complaints were re-examined and information about the further course of their brain fog was clarified.

MATERIALS AND METHODS

Subjects

All adult patients who applied with neurological complaints after COVID-19 were screened. The exclusion criteria were a diagnosis of dementia, malignancy, brain surgery, or other central nervous system diseases in the pre-pandemic period.

The diagnosis of COVID-19 in all patients was confirmed by polymerase chain reaction from nasopharyngeal swab samples. Among these patients, those who described brain fog were identified. A neurocognitive test battery was applied to those patients who agreed to a detailed examination. A control group of age-matched healthy individuals was used for comparison.

Informed consent was obtained from all participants. This study was carried out in accordance with the Declaration of Helsinki and under the approval of the TOBB University of Economics and Technology Faculty of Medicine Clinical Research Ethics Committee (approval number: 118/102-28/4/21).

Data Collection

Age, sex, time of SARS-CoV-2 infection, disease severity, the need for hospitalization, comorbidities, and current neurological complaints were recorded for all patients.

Neurocognitive assessment consisted of the following tests: the mini-mental test (MMSE), the enhanced cued recall test (recall test), the verbal fluency, the categorical fluency, digit span, recalling the months backward, clock-drawing, arithmetic operations, a trail making test, copying cubes, intersecting pentagons, and proverb interpretation. This battery of tests was applied to the patients and their age-matched controls. We aimed to evaluate the general mental states of the participants' memory, language skills, attention, complex attention, visuospatial skills, arithmetic skills, executive functions and abstract thinking skills. The mini-mental test was scored over 30 points, the recall test out of 48 points, the fluency tests by the number of words that could be counted in one minute, the digit span by the number of digits which could be repeated without error, the months backward test by the countdown time of the months (in seconds), the clock drawing test over 4 points, the arithmetic operations over 2 points, the abstract thinking over 2 points, the copying cubes and intersecting pentagons as "*fail*" or "*pass*", and the trail making tests were scored by time (in seconds).

For cases of clinical necessity, brain magnetic resonance imaging (MRI) of the patients were requested.

At the end of one year, the patients who had undergone neurocognitive testing were contacted by phone and questioned as to whether their cognitive complaints had persisted. Those patients whose complaints continued were invited to the department and re-evaluated with the same cognitive tests.

Statistical Analysis

Student's t-test was used to compare normally distributed parameters and the Mann-Whitney U test was used for non-normally distributed parameters. The chi-squared test was used to compare ratios. Analyses were performed using the SPSS v20 program. Results with $p<0.05$ were considered to be significant.

Results

General Characteristics of the Study Group

Between April, 2020 and September, 2021, ninety-five COVID-19 patients who applied with neurological complaints were identified (n=95). Of these, 40% had cognitive impairments (n=38). Sixteen of these patients agreed to further examination and to having a neurocognitive test battery. The mean age of the test group (n=16) was 37.4±13.0 years [standard deviation (SD)]. Four of the patients were male and 12 were female. The median years of education of the patients was 15 years

[interquartile range (IQR)=2]. All but two were infected during the pre-vaccination period and were treated with favipravir. Disease severity was found to be mild in 15 patients and moderate in one patient. The patient who had moderate COVID-19 was hospitalized for 12 days and received nasal oxygen therapy during this period. There were no patients who needed intensive care.

The mean age of the control group (n=15) was 36.7±11 (SD), and their median years of education was 15 years (IQR=4). There was no statistically significant difference between these parameters (p>0.05).

Neurocognitive Assessment

The cognitive test results of the patients and controls are given in Table 1.

It was seen that post-COVID patients were no different from the controls in terms of their general cognitive performance. There was no difference between the patients and the controls in their enhanced cued recall test total scores. When spontaneous recall was evaluated separately, it was observed that the patients had statistically significantly lower scores (p=0.03). Attention and complex attention skills assessed by digit span tests, as well as verbal language skills were found to be similar in the two groups. Although executive functions and central processing speed (trail making A, B and recalling the months backward tests) were lower in the patient group, the differences were not statistically significant (p=0.07; p=0.14 and p=0.22, respectively). There was no difference between the patients and the controls in their abstract thinking or visuospatial skills.

When the patient results were assessed individually rather than as a group, it was seen that almost all the results were "*normal*" according to the normative thresholds, and only one patient could not complete the trail making B-test. In other words, despite subjective complaints, post-COVID patients had no supra-threshold impairment reflected in the detailed cognitive test results.

There were 5 patients who underwent brain MRI after cognitive evaluation. No imaging findings were found in three of these patients. Non-specific hyper-intensities in the frontoparietal subcortical white matter were reported in one. In one patient, hyper-intense lesions were detected in the right frontoparietal and left callososeptal interface (Figure 1).

Clinical Follow-up

Sixteen patients who underwent neurocognitive evaluation were contacted by phone at the end of the first year. They were asked if their cognitive complaints had persisted. Except for one patient, all of the group stated that their complaints had disappeared after a few months (median 120 days) and they had recovered to their former state. Only one patient stated that his complaints still continued. This patient was invited to the outpatient clinic and the tests were repeated. It was observed that both the first tests and the second evaluation made one year later were within normal limits and did not show any temporal changes. It was discovered that this patient was also diagnosed with anxiety disorder and treatment was started.

DISCUSSION

This study revealed the following findings which may correspond to the daily cognitive complaints of post-COVID patients: i) Patients had normal "*encoding*", but spontaneous recall was significantly low. ii) There were differences between the patient groups, although not statistically significant, indicating a decrease in executive functions and mental processing speed. iii) Almost all of the patients were within the "*normal*" range when standard tests with normative data were used. iv) By the end of one year, the symptoms of brain fog had disappeared.

Memory dysfunction is one of the most frequently reported cognitive symptoms in the COVID-19 literature.[6,10,12,14,15] In this study, the enhanced cued recall test was applied to assess memory. This test is a validated memory test used successfully in Turkish samples.[16,17] It offers the chance to observe the patient's spontaneous recall and their recall with a cue. In our patient group, there was no difference in the total scores (total items remembered before and after the cue) when compared to the healthy controls. However, spontaneous recall was found to be significantly lower. In other words, the *learning* process took place in the patients' brains, but there was difficulty in accessing that information. As the secondary causes which may explain this difficulty,

Table 1. Neurocognitive test results of the patient and control groups

	Patients	Controls	p
MMSE, median (IQR)	30 (2)	30 (1)	0.48
Recall, median (IQR)	48 (1.5)	48 (1)	0.62
Recall spontaneous, median (IQR)	36.5 (7.8)	43 (3)	**0.03**
Digit span forward, median (IQR)	5.5 (2)	5 (1.25)	0.37
Digit span backward, median (IQR)	4 (3.25)	4 (2)	0.71
Phonemic fluency, median (IQR)	17 (6)	18 (5)	0.46
Categorical fluency median (IQR)	24 (5.5)	25 (6)	0.9
Months backward, median (IQR)	13.5 (9.8)	11.5 (4.5)	0.22
Clock drawing, median (IQR)	4 (1)	4 (0)	0.15
Arithmetic, median (IQR)	2 (1)	2 (0)	0.13
Trail making A, seconds median (IQR)	32 (24)	22.5 (13.5)	0.07
Trail making B, seconds median (IQR)	87 (79.5)	41.5 (67.8)	0.14
Abstract thinking, median (IQR)	2 (0)	2 (0)	0.39
Copying cubes and intersecting pentagons	pass	pass	1

MMSE: Mini-mental state examination, recall test: Enhanced cued recall test, IQR: Interquartile range.

factors such as attention, concentration and motivation should be considered. However, there was no significant difference in attention and complex attention criteria in our patient group when compared to the healthy controls. This suggests that the impairment is primarily the effect of COVID-19 on memory itself.

It was observed that our patients had relatively low central processing speeds and executive functions, but the differences in these domains did not reach statistical significance. Impairments in executive functions and attention areas have been frequently reported in COVID-19-related brain fog, therefore our patients' results being similar to our controls' results can be explained by our relatively small sample size.[6,12,14,15]

In a recent systematic review, the neurocognitive status in mild, moderate, severe COVID-19 and mixed patient groups were examined separately.[15] It was seen that 13 out of the 19 studies included in the review used first-level tests such as MoCA and MMSE. In two of the six studies in which second-level tests, i.e. detailed cognitive tests, were conducted, face-to-face standard evaluation was not possible and remote evaluation methods were applied. It was also evident that the specific cognitive tests used in these studies varied considerably. There were different findings about the relationship between cognitive complaints and COVID-19 severity. There are some studies suggesting that cognitive impairment was more common in cases of severe disease; some saying that it was more common in mild-moderate cases; and others saying it was independent of disease severity.[7,10,15] We think that it is important to evaluate mild COVID cases separately from severe cases in order to exclude post-intensive care syndrome. It is known that primary and secondary cognitive symptoms can develop just due to hospitalization in intensive care units.[18] Studies which evaluate mild COVID cases separately and qualify to enter into reviews are very few in number.[19,20] In addition, it was seen that general cognitive screening scales were used in these studies and there was no detailed neurocognitive examination data. In the study of Alemanno et al.[20], there were nine mild cases of COVID and the evaluation was made as early as 5-20 days. As can be seen, the literature on COVID-19-related brain fog is weak and limited. In our cohort, 16 patients were examined with detailed and *domain-specific* tests which were second level. These are standard tests which have been validated in Turkish society.

Ferrucci et al.[21] examined hospitalized COVID-19 patients with neuropsychological tests five months after discharge and found a decrease in mental processing speed in 41% of the patients. It was stated that the PO_2/FiO_2 value in the acute period was correlated with cognitive impairment, and cognitive deficits persisted at one-year follow-up.[21] We also observed a slight decrease in the central processing speeds in our own patients, but this difference was not significant. The fact that most of our patients were outpatients with mild disease severity without hypoxia may explain this difference. On the other hand, a global frequency reduction in EEG background activity (advanced analysis) at 4-6 months post-infectious was demonstrated in a pediatric sample of mild-to-moderate COVID cases.[22] In the aforementioned study, the patients did not clinically have central nervous system involvement due to COVID-19.[22] We think that the slowdown in global mental processes revealed by neuropsychological tests may be related to electrophysiological COVID findings.[23]

Arithmetic problem solving includes many cognitive steps. The recall of mathematical rules, associative recall, attention, sequencing, working memory and decision making are the main ones.[24] Despite the problems in performing calculations during daily life, our patients performed normally in these tests. This could be associated with higher attention and motivation during the neurocognitive testing, which is different from their daily routine. This points to the importance of *attention and vigilance* in mental arithmetic skills. In our patient group, no difference was found in visuospatial skills, abstract thinking skills or language-fluency tests when compared to the controls.

Seventy five percent of our patients describing brain fog were women. This finding is consistent with the literature.[7] It is predicted that this neurobiological difference between the sexes will provide information in understanding the neurotropic properties of this virus. In addition, 87% of our patients presenting with brain fog came from the period before the vaccination program had started. After the initiation of the vaccination program, it was observed that the number of applications with cognitive complaints decreased significantly. This finding supports the observation that COVID vaccines reduce prolonged COVID syndrome.[25]

The underlying mechanism being unknown, our study revealed that

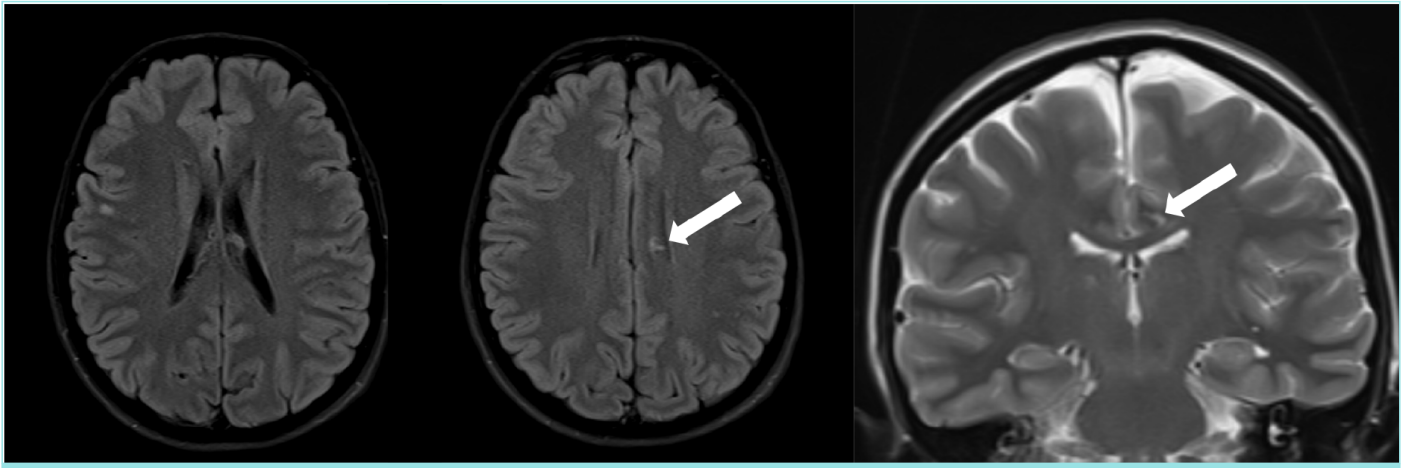

Figure 1. FLAIR images of a patient, right frontoparietal and left callososeptal (white arrows) hyper-intense lesions. The complaints of this 35-year-old patient were the inability to remember things to do, forgetting topics discussed at work in a short time, headaches and feelings of instability.

cognitive complaints disappeared in our patients and the patients had returned to their basal performances in daily life by the end of one year. We think that our data will provide an objective contribution to the COVID-associated brain fog literature for millions of people, especially those with mild cases.

Study Limitations

The neurocognitive test battery used in this study lasts approximately 45 minutes, but it may take longer depending on the patient's performance. This period resulted in a low number of patients who agreed to participate in these tests. Although there were 38 patients presenting with cognitive complaints, only 16 of them could be evaluated in detail. This relatively small sample size may have resulted in the statistical insignificance of the differences in the trail making test results.

Evaluating cognitive performance with normative references or controls may not be sufficient to detect actual changes in patients. This becomes more important in those patients with a high pre-morbid cognitive level. Ideally, patients should be assessed with their pre-COVID-19 and post-COVID-19 cognitive tests. Such a study design can only be achieved by using cognitive data obtained for other projects or large national databases.[19,26]

CONCLUSION

As of August, 2022, the SARS-CoV-2 pandemic had affected 590 million patients in the world and more than 16 million in our country (Türkiye). Residual respiratory diseases, severe or critically ill patients with many complications, will result in a serious disease burden in the chronic period of the pandemic. In addition, brain fog, which is a component of the long COVID-19 picture, appearing even after mild COVID-19, has taken its place as one of the important issues of the subacute and chronic processes. This study revealed the neurocognitive profiles of patients experiencing COVID-19-related brain fog in comparison to healthy controls. In our patient group, most of which consisted of mild COVID-19 cases, spontaneous recall was significantly lower, and there was a trend towards slowing in the central processing speeds and executive functions. By the one-year follow-up, COVID-associated brain fog had disappeared. It will be possible to elucidate all aspects of this clinical picture and to determine its relationship with neurodegenerative processes with larger-scale, longitudinal studies and pathological data.

MAIN POINTS

- Patients with post-COVID brain fog had normal *encoding*, but spontaneous recall was significantly low.
- There were decreases in executive functions and mental processing speeds in the patient group, although this was not statistically significant.
- Almost all of the patients were within the "*normal*" range when standard tests with normative data were used.
- By the end of one year, the symptoms of brain fog had disappeared.

Acknowledgments: The author would like to thank all the participants who contributed to this research by giving their consent.

ETHICS

Ethics Committee Approval: This study was carried out in accordance with the Declaration of Helsinki and under the approval of the TOBB University of Economics and Technology Faculty of Medicine Clinical Research Ethics Committee (approval number: 118/102-28/4/21).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Taskiran-Sag A, Eroğlu E, Canlar Ş, Poyraz BM, Özülken K, Mumcuoğlu T, et al. Subacute neurological sequelae in mild COVID-19 outpatients. Tuberk Toraks. 2022; 70(1): 27-36.
2. Tabacof L, Tosto-Mancuso J, Wood J, Cortes M, Kontorovich A, McCarthy D, et al. Post-acute COVID-19 Syndrome Negatively Impacts Physical Function, Cognitive Function, Health-Related Quality of Life, and Participation. Am J Phys Med Rehabil. 2022; 101(1): 48-52.
3. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimers Res Ther. 2020; 12(1): 69.
4. Apple AC, Oddi A, Peluso MJ, Asken BM, Henrich TJ, Kelly JD, et al. Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19. Ann Clin Transl Neurol. 2022; 9(2): 221-6.
5. Hellmuth J, Barnett TA, Asken BM, Kelly JD, Torres L, Stephens ML, et al. Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients. J Neurovirol. 2021; 27(1): 191-5.
6. Almeria M, Cejudo JC, Sotoca J, Deus J, Krupinski J. Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. Brain Behav Immun Health. 2020; 9: 100163.
7. Asadi-Pooya AA, Akbari A, Emami A, Lotfi M, Rostamihosseinkhani M, Nemati H, et al. Long COVID syndrome-associated brain fog. J Med Virol. 2022; 94(3): 979-84.
8. Pavli A, Theodoridou M, Maltezou HC. Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals. Arch Med Res. 2021; 52(6): 575-81.
9. Hampshire A, Chatfield DA, MPhil AM, Jolly A, Trender W, Hellyer PJ, et al. Multivariate profile and acute-phase correlates of cognitive deficits in a COVID-19 hospitalised cohort. EClinicalMedicine. 2022; 47: 101417.
10. Woo MS, Malsy J, Pöttgen J, Seddiq Zai S, Ufer F, Hadjilaou A, et al. Frequent neurocognitive deficits after recovery from mild COVID-19. Brain Commun. 2020; 2(2): fcaa205.
11. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun. 2022; 101: 93-135.
12. Bertuccelli M, Ciringione L, Rubega M, Bisiacchi P, Masiero S, Del Felice A. Cognitive impairment in people with previous COVID-19 infection: A scoping review. Cortex. 2022; 154: 212-30.
13. Schilling C, Meyer-Lindenberg A, Schweiger JI. Cognitive disorders and sleep disturbances in long COVID. Der Nervenarzt. 2022; 93(8): 779-87.
14. Daroische R, Hemminghyth MS, Eilertsen TH, Breitve MH, Chwiszczuk LJ. Cognitive Impairment After COVID-19-A Review on Objective Test Data. Front Neurol. 2021; 12: 699582.
15. Biagianti B, Di Liberto A, Nicolò Edoardo A, Lisi I, Nobilia L, de Ferrabonc GD, et al. Cognitive Assessment in SARS-CoV-2 Patients: A Systematic Review.

Front Aging Neurosci. 2022; 14: 909661.

16. Gündüz H, Gündüz GB, Kaya H, Inal Ö, Gülveren H, Tavat BC. Norm Determination Study of Trail Making Test, Enhanced Cued Recall Test and Clock Drawing Test for Turkish Sample Between 6-18 Years of Age. Noro Psikiyatr Ars. 2021; 58(4): 314-20.
17. Saka E, Mihci E, Topcuoglu MA, Balkan S. Enhanced cued recall has a high utility as a screening test in the diagnosis of Alzheimer's disease and mild cognitive impairment in Turkish people. Arch Clin Neuropsychol. 2006; 21(7): 745-51.
18. Rawal G, Yadav S, Kumar R. Post-intensive Care Syndrome: an Overview. J Transl Int Med. 2017; 5(2): 90-2.
19. Del Brutto OH, Wu S, Mera RM, Costa AF, Recalde BY, Issa NP. Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort. Eur J Neurol. 2021; 28(10): 3245-53.
20. Alemanno F, Houdayer E, Parma A, Spina A, Del Forno A, Scatolini A, et al. COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. PLoS One. 2021; 16(2): e0246590.
21. Ferrucci R, Dini M, Rosci C, Capozza A, Groppo E, Reitano MR, et al. One-year cognitive follow-up of COVID-19 hospitalized patients. Eur J Neurol. 2022; 29(7): 2006-14.
22. Yılmaz A, Yayıcı Köken Ö, Şekeroğlu B, Şanlıdağ B. A Near-Global Slowing of Background Activity and Epileptic Discharges in Children with Mild to Moderately Symptomatic COVID-19 Infection: An Electro-Neurophysiological Study. Clin EEG Neurosci. 2022; 53(6): 532-42.
23. Anokhin A, Vogel F. EEG Alpha Rhythm Frequency and Intelligence in Normal Adults. Intelligence. 1996;23(1):1-14.
24. Menon V. Developmental cognitive neuroscience of arithmetic: implications for learning and education. ZDM. 2010; 42(6): 515-25.
25. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis. 2022; 22(1): 43-55.
26. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022; 604(7907): 697-707.

RESEARCH ARTICLE

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Evaluation of COVID-19 Anxiety and Phobia Levels of the Parents of Pediatric Patients Undergoing Surgery

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Abstract

BACKGROUND/AIMS: The purpose of this study was to evaluate the levels of coronavirus disease-2019 (COVID-19) anxiety and the phobia levels of the parents of pediatric patients who were scheduled to undergo surgery under general anesthesia in Turkey during the COVID-19 pandemic, and to examine the factors affecting these.

MATERIALS AND METHODS: The participants were asked to complete a socio-demographic data form, the Coronavirus Anxiety Scale (CAS), and the COVID-19 Phobia Scale (C19P-S). The effects on depression, anxiety, and health anxiety levels of factors such as the socio-demographic characteristics of the children and parents, and the supplementary data of the parents regarding the child's illness were then investigated.

RESULTS: In terms of CAS and C19P-S cut-off points, 4.7% (n=7) of the parents scored above the anxiety cut-off point and 17.4% (n=26) scored above the phobia cut-off point. Both CAS and C19P-S scores were higher for female parents, non-working parents, and those with higher education levels compared with male parents, employed parents, and those with lower education levels.

CONCLUSION: The results of this prospective, cross-sectional, observational study suggest that being female, non-working, and a having high level of education were risk factors for anxiety and phobia in the parents of pediatric patients related to COVID-19.

Keywords: Anxiety, coronavirus, SARS, parents, pediatric, phobia

INTRODUCTION

A pandemic which originated in the Wuhan region of China in December, 2019 was detected as a new type of coronavirus disease called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [coronavirus disease-2019 (COVID-19)]. The COVID-19 pandemic has seriously affected medical practice around the World.[1] Changes in routine clinical approaches in healthcare settings are necessary to reduce the risk of infections in patients, families, and healthcare providers, while balancing the dangers and benefits of delaying or changing routine patient care.[2] The American College of Surgeons (ACS) published guidelines recommending that all elective procedures should be delayed or performed in outpatient surgery centers if possible. The only exceptions are most oncologic and high-precision surgical procedures. According to guidance from the Turkish Ministry of Health, protocols for surgical procedures in Türkiye were changed radically due to the pandemic.[3] However, as delaying surgery for "time-sensitive" and emergency diseases may affect children's growth, development, and their quality of life, the ACS also published guidelines specifically on pediatric surgery, as well as their previous general recommendations, which applied to all surgical subspecialties.[4] As noted in other reports, many families were concerned about whether it was safe to bring their children to the hospital.[5,6]

Both the COVID-19 pandemic and the surgical procedure to be performed affect symptoms of anxiety, fear or acute stress disorder for the children and their families. As the disease spread, investigators

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started to emphasize the importance of protecting mental health.[7,8] Identifying factors which contribute to significant preoperative anxiety levels in pediatric patients and their parents can help healthcare professionals choose the most appropriate strategy for anxiety control from a variety of alternative strategies. However, when the literature was examined, no studies had examined both COVID-19 anxiety and the phobia levels of those families with children who received general anesthesia during the COVID-19 pandemic. Therefore, this study was planned to evaluate the COVID-19 anxiety and phobia levels of the parents of pediatric patients who were scheduled to undergo surgery under general anesthesia in Türkiye.

MATERIALS AND METHODS

This study was a prospective, cross-sectional, observational study. The population of the study consisted of those parents of pediatric patients who were scheduled for surgery under general anesthesia between May, 2020 and September, 2020 at Selçuk University Faculty of Medicine, Department of Anesthesiology and Reanimation. The Selçuk University Faculty of Medicine Ethical Committee approval was received (approval number: 2020/17). Written informed consent was obtained from all participants. This study was registered with the clinical trials registry (www.ClinicalTrials.gov. identifier NCT04631172). The parents of pediatric patients with American Society of Anesthesiologists (ASA) classification I-II, aged 1-12 years who were administered anesthesia to undergo surgery between the specified dates were included in this study without using any sample selection. The parents of those children with ASA III or higher risk, of those expected to have difficult intubation, of those with serious complications related to intraoperative anesthesia (e.g. respiratory depression, myocardial depression, cardiac arrhythmia, bronchospasm, laryngospasm, anaphylactic reaction, hypotension, bleeding), and of those who could not communicate were excluded from this study. The data were obtained from only one of the parents through a face-to-face interview before the child was taken to surgery after the necessary explanations had been made by the researchers. To enable the parents to answer the questions easily, a separate room in the relevant clinic was used for the interviews. The characteristics of the children and the parents, the supplementary data of the parents regarding the child's illness, and their contact information were obtained. The sample size was based on an estimated prevalence of 6.3% determined in the study of Wang et al.[9] In order to reach 95% power at a 5% significance level, the required sample volume for a 4% deviation from this estimated prevalence was calculated to be 142. The sample size allowing for possible data loss was determined to be 155 patients. Power analysis was performed using the "pwr" package in R 3.6.0 (https://www.r-project.org).

Data Collection Process and Procedure

The Coronavirus Anxiety Scale (CAS), which was developed by Lee[8] and validated in Turkish by Evren et al.[10] was used to evaluate COVID-19 anxiety levels. In the validation study, the Cronbach's alpha of the Turkish version of CAS was 0.87. In the present study, Cronbach's alpha was 0.89. This result of the study showed that the CAS was highly reliable. CAS is a 5-point Likert-type scale. The scale consists of five questions and one dimension. Scoring of the scale is evaluated as 0: never, 1: rarely, less than one or two days, 2: a few days, 3: more than a week, and 4: almost every day in the last two weeks. The total score ranges from 0 to 20. Lee[8] determined a CAS cut-off score of 9 in order to distinguish between those with dysfunctional anxiety and those without anxiety.

The COVID 19 phobia scale (C19P-S) is a 20-item, 4-subdimension (*psychological*, *somatic*, *social* and *economic*) scale in which items are answered in a 5-point response format developed by Arpaci et al.[11] in order to measure the phobias which may develop regarding COVID-19. In the validation study, the Cronbach's alpha of the Turkish version of C19P-S was 0.92. In the present study, Cronbach's alpha was 0.94. The results of this study demonstrated that the C19P-S was exceptionally reliable. The scale items are scored between 1 = "strongly disagree" and 5 = "strongly agree". Sub-dimension scores are obtained by the sum of the points of the answers given to the items belonging to that sub-dimension, while the total C19P-S score is obtained by the total of the sub-dimension scores, ranging between 20 and 100 points. The total scores are obtained by summing the scores of both scales separately (CAS = 0-20, C19P-S = 20-100). Due to the absence of sufficient studies, a cut-off point of 65 was determined.[11] Higher scores indicate greater anxiety levels.

Statistical Analysis

Statistical analyses were performed using the SPSS 21.0 software (SPSS Institute, Chicago, IL, USA). Parametric data were tested using Student's t-test or ANOVA and the data are presented as means and standard errors with 95% confidence intervals (CI). A p-value <0.05 was considered to be statistically significant.

RESULTS

Of the 155 parents invited onto this study, 149 parents (96%) who agreed to participate completed the questionnaire and so were included in our analysis. Overall, 108 (72%) of the parents participating in this study were female and 41 (28%) were male. The participants' mean age was 33.4±7.5 years. The child group undergoing anesthesia consisted of 65 (44%) girls and 84 (56%) boys whose mean age was 5.6±4.1 years. Further child and parental socio-demographic data and complementary data regarding the parents and the child's disease are shown in Table 1.

Table 2 shows the CAS and C19P-S levels in relation to the socio-demographic data. The mean CAS and C19P-S scores of the parents were 0.24±0.53 and 2.33±0.82, respectively. There were seven (4.7%) parents who exceeded the CAS cut-off level (>9). For C19P-S, there were 26 (17.4%) parents who exceeded the cut-off level (>65).

When the results of the parents according to their gender were evaluated, CAS in females was significantly higher than in males [2.63±0.37, 95% CI: (1.89-3.36)] vs. [0.73±0.27, 95% CI: (0.18-1.28); p=0.002, respectively]. In parallel, female parents (mothers) displayed significantly higher levels of C19P-S than their male counterparts (fathers) [48.52±1.55, (95% CI: 45.45-51.60)] vs. [41.92±2.69, 95% CI: (36.46-7.37); p=0.022, respectively]. Also, as shown in Table 2, highly educated (high school and university) parents had higher CAS (p=0.007) and C19P-S (p=0.037) when compared with those who had lower levels of education (illiterate, primary and middle school). The CAS [2.76±0.39, 95% CI: (1.97-3.54)] and C19P-S [49.70±1.66, 95% CI: (46.16-52.77)] levels of the non-working parents were higher than those of the working parents [CAS: 0.87±0.25, 95% CI: (0.33-1.37) and C19P-S: 41.40±2.03, 95% CI: (37.31-45.49), respectively] (p=0.001, p=0.002, respectively). Finally, there was no statistical difference according to CAS and C19P-S regarding the child's characteristics, age group, place of residence, number of siblings, social security status, the presence of psychological problems, having previously encountered patients with COVID-19, being aware of the child's diagnosis, previous experience of hospitalization, having information about the child's surgery, and requesting information about COVID-19 (p>0.05).

Table 1. Socio-demographic and complementary characteristics of the parents			
Child's characteristics		**n**	**%**
Age group	0-1	34	22.9
	2-6	56	37.6
	>7	59	39.6
Gender	Female	65	43.6
	Male	84	56.4
Duration of illness (days)	0-30	54	36.2
	>30	95	63.8
Number of hospitalizations	1	77	51.7
	>2	72	48.3
Preoperative hospitalization time (days)	1	104	69.8
	2-6	30	29.1
	>7	15	10.1
Parental characteristics			
Age group	<20	9	6.0
	20-29	45	30.2
	30-39	61	40.9
	>40	34	22.9
Gender	Female	108	72.5
	Male	41	27.5
Place of residence	Urban	93	62.4
	Town	38	25.5
	Rural	18	12.1
Number of children	1	42	28.2
	2	51	34.2
	>3	56	37.6
Educational status	Illiterate	7	4.7
	Primary school	41	27.5
	Middle school	38	25.5
	High school	33	22.1
	University	30	20.7
Working after the pandemic	Yes	49	32.9
	No	100	67.1
Health insurance status	Yes	106	71.1
	No	43	28.9
The presence of psychological problems	Yes	16	10.7
	No	133	89.3
Have you seen COVID-19 patients before?	Yes	137	91.9
	No	12	8.1
Parent's information about their child's illness			
Knowledge of the child's diagnosis	Yes	130	87.2
	No	19	12.8
Previous experience of hospitalization	Yes	92	61.7
	No	57	38.3
Having information about the child's surgery	Yes	121	81.2
	No	28	18.8
Who provided the information	Nurse	20	13.4
	Anesthesiologist	16	10.7
	Unit doctor	113	75.8

Table 1. Continued

Child's characteristics		n	%
Has enough information been obtained about the child's surgery?	Yes	127	85.2
	No	22	14.8
Requesting information about Coronavirus disease-2019	Yes	37	24.8
	No	112	75.2
Has sufficient information been obtained about Coronavirus disease-2019 infection?	Yes	95	63.8
	No	54	36.3

Table 2. Comparison of the mean CAS and C19P-S levels within the group according to the socio-demographic and complementary characteristics of the parents

CAS					CP19-S		
		Mean ± SE	(95% CI)	p	Mean ± SE	(95% CI)	p
Child's characteristics							
Age group	0-1	2.17±0.75	(0.63-3.72)	0.771	46.55±3.33	(39.76-53.34)	0.694
	2-6	2.10±0.40	(1.29-2.92)		46.03±1.81	(42.39-49.68)	
	>7	2.13±0.43	(1.25-3.01)		47.71±2.19	(43.31-52.10)	
Gender	Female	2.06±0.40	(1.24-2.88)	0.964	44.78±2.02	(40.74-48.82)	0.150
	Male	2.19±0.40	(1.39-2.98)		48.39±1.76	(44.57-51.91)	
Duration of illness (days)	0-30	2.61±0.56	(1.47-3.74)	0.340	49.33±2.21	(44.89-53.77)	0.221
	>30	1.86±0.31	(1.24-2.48)		45.38±1.66	(42.08-48.69)	
Number of hospitalizations	1	2.46±0.44	(1.57-3.36)	0.377	48.28±1.87	(44.54-52.02)	0.242
	>2	1.77±0.34	(1.08-2.47)		45.25±1.89	(41.47-49.02)	
Preoperative hospitalization time (day)	1	2.49±0.36	(1.76-3.21)	0.092	47.93±1.71	(44.52-51.32)	0.516
	2-6	1.13±0.37	(0.35-1.91)		43.80±2.30	(39.09-48.50)	
	>7	1.66±1.02	(0.53-3.86)		45.20±3.62	(37.41-32.98)	
Parental characteristics							
Age group	<20	0.21±0.11	(0.04-0.36)	0.063	47.28±7.57	(28.75-65.81)	0.505
	20-29	2.95±0.63	(1.68-4.22)		50.06±2.54	(44.94-55.18)	
	30-39	2.26±0.40	(1.44-3.07)		48.65±2.14	(44.37-52.94)	
	>40	1.35±0.54	(0.25-2.45)		41.55±2.37	(36.72-46.39)	
Gender	Female	2.63±0.37	(1.89-3.36)	**0.002***	48.52±1.55	(45.45-51.60)	**0.022***
	Male	0.73±0.27	(0.18-1.28)		41.92±2.69	(36.46-47.37)	
Place of residence	Urban	1.97±0.33	(1.30-2.65)	0.055	48.21±1.61	(45.00-51.42)	0.244
	Town	3.15±0.71	(1.71-4.60)		45.97±3.15	(39.57-53.37)	
	Rural	0.77±0.40	(0.06-1.62)		41.38±2.69	(35.70-47.07)	
Number of children	1	3.00±0.72	(1.53-4.46)	0.125	50.52±2.93	(44.59-56.45)	0.077
	2	2.21±0.42	(1.35-3.07)		48.66±2.33	(43.98-53.34)	
	>3	1.43±0.35	(0.72-2.14)		42.54±1.70	(39.13-45.96)	
Educational status	Illiterate	1.57±1.02	(0.92-4.06)	**0.007***	38.00±3.83	(29.15-46.84)	**0.037***
	Primary school	0.90±0.26	(0.36-1.44)		43.68±2.04	(39.54-47.81)	
	Middle school	1.50±0.40	(0.67-2.32)		46.65±2.55	(41.40-51.91)	
	High school	3.12±066	(1.77-4.47)		49.54±3.03	(43.37-55.72)	
	University	4.07±1.01	(1.97-6.17)		50.11±3.55	(42.81-57.41)	
Working after the pandemic	Yes	0.87±0.25	(0.33-1.37)	**0.001***	41.40±2.03	(37.31-45.49)	**0.002***
	No	2.76±0.39	(1.97-3.54)		49.70±1.66	(46.16-52.77)	
Health insurance status	Yes	2.29±0.37	(1.55-3.03)	0.828	46.72±1.51	(43.72-49.72)	0.895
	No	1.74±0.38	(0.97-2.51)		47.70±2.75	(41.47-52.61)	
Any psychological problems	Yes	2.75±1.05	(0.51-4.99)	0.848	44.06±5.63	(32.05-56.07)	0.169
	No	2.06±0.29	(1.47-2.64)		47.15±1.34	(44.49-49.80)	

Table 2. Continued

		CAS			CP19-S		
		Mean ± SE	(95% CI)	p	Mean ± SE	(95% CI)	p
Have you seen COVID-19 patients before?	Yes	3.75±1.16	(1.19-6.30)	0.081	54.33±5.26	(42.74-65.92)	0.112
	No	1.59±0.29	(1.41-2.57)		46.16±1.36	(43.45-48.86)	
Parent's information about the child's illness							
Knowledge of the child's diagnosis	Yes	2.26±0.30	(1.65-2.86)	0.054	47.46±1.47	(44.53-50.38)	0.232
	No	1.26±0.82	(0.47-3.00)		42.42±2.56	(37.03-47.81)	
Previous experience of hospitalizations	Yes	1.97±0.34	(1.29-2.66)	0.587	46.47±1.74	(43.00-49.95)	0.942
	No	2.38±0.31	(1.36-3.40)		47.36±2.06	(43.43-51.50)	
Obtaining information about the child's surgery	Yes	2.17±0.31	(1.54-2.80)	0.672	46.47±1.48	(43.54-49.40)	0.446
	No	2.03±0.68	(0.63-3.44)		48.55±3.23	(41.90-55.21)	
Who provided the information	Nurse	2.65±0.93	(0.69-4.60)	0.733	46.85±3.52	(39.47-54.22)	0.979
	Anesthesiologist	1.12±0.44	(0.17-2.07)		47.50±3.67	(39.60-55.33)	
	Unit doctor	2.18±0.33	(1.52-2.84)		46.71±1.57	(43.60-49.83)	
Has enough information been obtained about the child's surgery?	Yes	2.26±0.32	(1.62-2.86)	0.144	47.37±1.45	(44.50-30.25)	0.186
	No	1.38±0.61	(0.09-2.67)		42.90±3.45	(35.70-50.10)	
Has sufficient information been given about COVID-19 infection?	Yes	2.70±0.57	(1.54-3.86)	0.238	51.51±2.98	(45.45-57.56)	0.083
	No	2.13±0.54	(1.29-2.60)		45.26±1.45	(43.33-52.70)	
Requesting information about COVID-19	Yes	2.14±0.33	(1.47-2.82)	0.724	46.31±1.65	(43.03-49.69)	0.513
	No	1.97±0.33	(1.03-3.23)		48.01±2.33	(42.38-48.15)	
Age of parent interviewed	<20	0.21±0.11	(0.04-0.36)	0.063	38.00±3.83	(29.15-46.84)	0.055
	20-29	2.95±0.63	(1.68-4.22)		50.06±2.54	(44.94-55.18)	
	30-39	2.26±0.40	(1.44-3.07)		48.65±2.14	(44.37-52.94)	
	>40	1.35±0.54	(0.25-2.45)		41.55±2.37	(36.72-46.39)	
Gender of parent	Female	2.63±0.37	(1.89-3.36)	0.002	48.52±1.55	(45.45-51.60)	0.022
	Male	0.73±0.27	(0.18-1.28)		41.92±2.69	(36.46-47.37)	
Place of residence	Urban	1.97±0.33	(1.30-2.65)	0.055	48.21±1.61	(45.00-51.42)	0.244
	Town	3.15±0.71	(1.71-4.60)		45.97±3.15	(39.57-53.37)	
	Rural	0.77±0.40	(0.06-1.62)		41.38±2.69	(35.70-47.07)	
Number of children	1	3.00±0.72	(1.53-4.46)	0.125	50.52±2.93	(44.59-56.45)	0.077
	2	2.21±0.42	(1.35-3.07)		48.66±2.33	(43.98-53.34)	
	3 or more	1.43±0.35	(0.72-2.14)		42.54±1.70	(39.13-45.96)	
Parental educational status	Illiterate	1.57±1.02	(0.92-4.06)	0.007	47.28±7.57	(28.75-65.81)	0.607
	Primary school	0.90±0.26	(0.36-1.44)		43.68±2.04	(39.54-47.81)	
	Middle school	1.50±0.40	(0.67-2.32)		46.65±2.55	(41.40-51.91)	
	High School	3.12±066	(1.77-4.47)		49.54±3.03	(43.37-55.72)	
	University	4.07±1.01	(1.97-6.17)		50.11±3.55	(42.81-57.41)	
Employment status of the parent	1	0.87±0.25	(0.33-1.37)	0.001	41.40±2.03	(37.31-45.49)	0.002
	2	2.76±0.39	(1.97-3.54)		49.70±1.66	(46.16-52.77)	
Social security status of the parent	Working	2.29±0.37	(1.55-3.03)	0.828	46.72±1.51	(43.72-49.72)	0.895
	Non-working	1.74±0.38	(0.97-2.51)		47.70±2.75	(41.47-52.61)	
Presence of psychological problems	Present	2.75±1.05	(0.51-4.99)	0.848	44.06±5.63	(32.05-56.07)	0.169
	Absent	2.06±0.29	(1.47-2.64)		47.15±1.34	(44.49-49.80)	
Have you seen someone with COVID-19 before	No	1.59±0.29	(1.41-2.57)	0.081	46.16±1.36	(43.45-48.86)	0.112
	Yes	3.75±1.16	(1.19-6.30)		54.33±5.26	(42.74-65.92)	
Knowledge regarding the diagnosis of the child	Yes	2.26±0.30	(1.65-2.86)	0.054	47.46±1.47	(44.53-50.38)	0.232
	No	1.26±0.82	(0.47-3.00)		42.42±2.56	(37.03-47.81)	
Previous experience of hospitalization	Yes	1.97±0.34	(1.29-2.66)	0.587	46.47±1.74	(43.00-49.95)	0.942
	No	2.38±0.31	(1.36-3.40)		47.36±2.06	(43.43-51.50)	

Table 2. Continued

CAS					CP19-S		
		Mean ± SE	(95% CI)	p	Mean ± SE	(95% CI)	p
Information regarding the surgery to be performed	Given	2.17±0.31	(1.54-2.80)	0.672	46.47±1.48	(43.54-49.40)	0.446
	Not given	2.03±0.68	(0.63-3.44)		48.55±3.23	(41.90-55.21)	
Source of information	Nurse	2.65±0.93	(0.69-4.60)	0.733	46.85±3.52	(39.47-54.22)	0.979
	Anesthetist	1.12±0.44	(0.17-2.07)		47.50±3.67	(39.60-55.33)	
	Doctor	2.18±0.33	(1.52-2.84)		46.71±1.57	(43.60-49.83)	
Sufficient information given	Sufficient	2.26±0.32	(1.62-2.86)	0.144	47.37±1.45	(44.50-30.25)	0.186
	Insufficient	1.38±0.61	(0.09-2.67)		42.90±3.45	(35.70-50.10)	
Have you received information about the COVID-19 transmission?	Yes	2.14±0.33	(1.47-2.82)	0.724	46.31±1.65	(43.03-49.69)	0.513
	No	2.13±0.54	(1.03-3.23)		48.01±2.33	(43.33-52.70)	
Have you requested information about COVID-19	Yes	2.70±0.57	(1.54-3.86)	0.238	51.51±2.98	(45.45-57.56)	0.083
	No	1.97±0.33	(1.29-2.60)		45.26±1.45	(42.38-48.15)	

CAS: Coronavirus Anxiety Scale, C19P-S: COVID-19 Phobia Scale, mean ± SE: means ± standard error, CI: Confidence interval, *p<0.05, COVID-19: Coronavirus disease-2019.

DISCUSSION

The major unexpected finding of our study according to both scales was that, despite the increase in the number cases of COVID-19, the parents of children who were going to be anesthetized had low levels of COVID-19 anxiety and phobia levels. However, it was observed that female, non-working, and highly educated parents had higher COVID-19 anxiety and phobia than their male, employed, and poorly educated counterparts.

As the number of COVID-19 cases increases, so does the chance of life-threatening SARS-CoV-2 exposure. This can exacerbate uncertainty and increase concerns about contracting the virus. Individuals are afraid of the virus and worry about the health of their loved ones. Symptoms such as anxiety, depression, fear, stress, and sleep problems have become more common during the COVID-19 pandemic.[12,13] Indeed, the prevalence of depression, anxiety, and post-traumatic stress disorder symptoms were reported as being between 10% and 18% during and after the SARS pandemic.[14] Additionally, the pandemic has triggered fear among individuals, which makes it very important to understand the impact of this crisis on people's mental health.[15] The depression and anxiety levels and rates (23.6% and 45.1%, respectively) are expected findings when considering pandemic-related psychological effects. A comprehensive study from China reported that about 35% of people were psychologically affected by the pandemic.[16] Findings of higher incidences of depression and anxiety in individuals with a history of psychiatric illness may also be associated with the recurrence of psychiatric diseases before and after the pandemic, as shown in previous studies of this type.[17] A recent study by Yuan et al.[18] showed that anxiety in the parents of children hospitalized during the COVID-19 pandemic was higher than before the pandemic. It was surprising that in our study, COVID-19 anxiety remained as low as 4.7% and phobia at 17.4%.

The prevalence of anxiety in females appears to be higher than in males.[19,20] In the COVID-19 pandemic, females have also been reported to have higher levels of anxiety related to the pandemic.[16,21,22] In the study by Zhong et al.[23], even though females had better knowledge of the disease and followed recommendations such as wearing masks and social distancing more than males, the uncertainty of whether the pandemic could be controlled affected them more. In another study, anxiety disorder was seen at a three-times higher level in women than in men during the COVID-19 pandemic.[9] High health anxiety can leave a person vulnerable to negative emotional states such as anxiety and depression. In light of our current knowledge, high levels of anxiety, depression, and health anxiety in women in this study are not an unexpected finding. In the present study, COVID-19 anxiety and phobias among the female parents were higher than in the male parents. This may be a reflection of the increased burden of care responsibilities placed on women.

Some studies demonstrated that non-working parents had more anxiety and fear due to their lower household income.[24,25] The higher CAS and corona phobia levels of the non-workers in this study can be considered to be as a result of the economic conditions in our country on the family.

The results in the literature are contradictory in terms of the relationships between people's knowledge regarding viral pandemics and their health anxiety. Several studies have shown that a higher level of knowledge about the virus is associated with increased anxiety[26,27], whereas other studies found that more information was associated with less anxiety.[28] Wang et al.[29] reported that there was no significant relationship between people's information about the virus and their anxiety. These disparate results may depend on the type, content, source, purpose, and/or scope of the media or information source. In another study, it was reported that mothers with low education levels had difficulty in understanding the reasons for the changes in their children's condition, and therefore their anxiety levels were high.[30] In this study, there appears to be a positive correlation between the parents' higher educational backgrounds such as high school and university and their anxiety and phobia levels. One possible explanation for this could be that as the individual's intellectual level increases, their more detailed understanding of the COVID-19 pandemic and the potential risks of anesthesia may increase their anxiety and phobia. On the other hand, it was interesting that parents with low educational backgrounds had low levels of anxiety and phobia, which may be due to their lack of knowledge.

Study Limitations

This study has both strengths and limitations. The major strength is that it was the first study to measure COVID-19 anxiety and phobia together; the questionnaires were validated in Turkish and they were

completed in face-to-face interviews. In terms of its limitations, firstly, it was a single-center study, and the study population consisted of a homogeneous region in terms of its Turkish population and it did not include racial/ethnic subgroups. If this study had been conducted in a multicenter fashion, its effectiveness and patient population would have been higher. In this way, parents in cities (such as İstanbul, Ankara) with a high incidence of COVID-19 at the clinical level could have been included in our data. Another issue could be the differences in the COVID-19 process occurring over the period of our study, given its 3-month working time. However, in this process, the fact that COVID-19 data were relatively horizontal in our country may have eliminated any differences caused by potential changes during our study period.

CONCLUSION

This study found that the COVID-19 anxiety and phobia levels of the parents of pediatric patients who underwent surgery under general anesthesia during the COVID-19 pandemic were low. However, according to socio-demographic variables, it was shown that female parents, non-working parents, and those with a higher level of education were more severely affected by COVID-19 anxiety and phobia than the other parents. Therefore, these variables should be kept in mind in future psychiatric planning.

MAIN POINTS

- Both the COVID-19 pandemic and the surgical procedure are reflected in the symptoms of anxiety, fear or acute stress disorder of children and their families. However, it was surprising that in our study, COVID-19 anxiety remained as low as 4.7% and phobia at 17.4%.
- Female parents displayed significantly higher levels of C19P-S and CAS than males.
- The CAS levels of non-working parents were higher than those of working parents.

ETHICS

Ethics Committee Approval: The Selçuk University Faculty of Medicine Ethical committee approval was received (approval number: 2020/17).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.C., Design: F.Ç., Supervision: M.S., İ.K., Fundings: F.Ç., Materials: F.Ç., Data Collection and/or Processing: F.Ç., M.S.U., E.A., P.Ş., A.S., Analysis and/or Interpretation: M.S., Literature Search: M.S.U., M.S., E.A., P.Ş., A.S., İ.K., Writing: F.Ç., Critical Review: İ.K.

DISCLOSURES

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

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REFERENCES

1. Ducournau F, Arianni M, Awwad S, Baur EM, Beaulieu JY, Bouloudhnine M, et al. COVID-19: Initial experience of an international group of hand surgeons. Hand Surg Rehabil. 2020; 39(3): 159-66.
2. Farrell S, Schaeffer EK, Mulpuri K. Recommendations for the Care of Pediatric Orthopaedic Patients During the COVID-19 Pandemic. J Am Acad Orthop Surg. 2020; 28(11): e477-86.
3. American College of Surgeons. COVID-19: Guidance for Triage of Non-Emergent Surgical Procedures [Internet]. American College of Surgeons [cited 2020 Apr 11]. Available from: https://www.facs.org/covid-19/clinical-guidance/triage.
4. American College of Surgeons. COVID-19 Guidelines for Triage of Pediatric Patients [Internet]. American College of Surgeons [cited 2020 Apr 11]. Available from: https://www.facs.org/for-medical-professionals/covid-19/clinical-guidance/elective-case/pediatric-surgery/
5. Davenport M, Pakarinen MP, Tam P, Laje P, Holcomb GW 3rd. From the editors: The COVID-19 crisis and its implications for pediatric surgeons. J Pediatr Surg. 2020; 55(5): 785-8.
6. Children Hospital Los Angeles. https://www.chla.org/blog/hospital-news/covid-19-information-patients-parents-and-visitors Accessed on June 6, 2020.
7. Bakioğlu F, Korkmaz O, Ercan H. Fear of COVID-19 and Positivity: Mediating Role of Intolerance of Uncertainty, Depression, Anxiety, and Stress. Int J Ment Health Addict. 2021; 19(6): 2369-82.
8. Lee SA. Coronavirus Anxiety Scale: A brief mental health screener for COVID-19 related anxiety. Death Stud. 2020; 44(7): 393-401.
9. Wang Y, Di Y, Ye J, Wei W. Study on the public psychological states and its related factors during the outbreak of coronavirus disease 2019 (COVID-19) in some regions of China. Psychol Health Med. 2021; 26(1): 13-22.
10. Evren C, Evren B, Dalbudak E, Topcu M, Kutlu N. Measuring anxiety related to COVID-19: A Turkish validation study of the Coronavirus Anxiety Scale. Death Stud. 2022; 46(5): 1052-8.
11. Arpaci I, Karataş K, Baloğlu M. The development and initial tests for the psychometric properties of the COVID-19 Phobia Scale (C19P-S). Pers Individ Dif. 2020; 164: 110108.
12. Torales J, O'Higgins M, Castaldelli-Maia JM, Ventriglio A. The outbreak of COVID-19 coronavirus and its impact on global mental health. Int J Soc Psychiatry. 2020; 66(4): 317-20.
13. Ahorsu DK, Lin CY, Imani V, Saffari M, Griffiths MD, Pakpour AH. The Fear of COVID-19 Scale: Development and Initial Validation. Int J Ment Health Addict. 2022; 20(3): 1537-45.
14. Wu KK, Chan SK, Ma TM. Posttraumatic stress, anxiety, and depression in survivors of severe acute respiratory syndrome (SARS). J Trauma Stress. 2005; 18(1): 39-42.
15. Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry. 2020; 7(3): 228-9.
16. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. Gen Psychiatr. 2020; 33(2): e100213. Erratum in: Gen Psychiatr. 2020; 33(2): e100213corr1.
17. Lee AM, Wong JG, McAlonan GM, Cheung V, Cheung C, Sham PC, et al. Stress and psychological distress among SARS survivors 1 year after the outbreak. Can J Psychiatry. 2007; 52(4): 233-40.
18. Yuan R, Xu QH, Xia CC, Lou CY, Xie Z, Ge QM, et al. Psychological status of parents of hospitalized children during the COVID-19 epidemic in China. Psychiatry Res. 2020; 288: 112953.

19. Alexander JL, Dennerstein L, Kotz K, Richardson G. Women, anxiety and mood: a review of nomenclature, comorbidity and epidemiology. Expert Rev Neurother. 2007; 7(11 Suppl): S45-58.

20. Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015; 40(4): 219-21.

21. Moghanibashi-Mansourieh A. Assessing the anxiety level of Iranian general population during COVID-19 outbreak. Asian J Psychiatr. 2020; 51: 102076.

22. Jungmann SM, Witthöft M. Health anxiety, cyberchondria, and coping in the current COVID-19 pandemic: Which factors are related to coronavirus anxiety? J Anxiety Disord. 2020; 73: 102239.

23. Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among Chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. Int J Biol Sci. 2020; 16(10): 1745-52.

24. Cameron EE, Joyce KM, Delaquis CP, Reynolds K, Protudjer JLP, Roos LE. Maternal psychological distress & mental health service use during the COVID-19 pandemic. J Affect Disord. 2020; 276: 765-74.

25. Ahmed F, Ahmed N, Pissarides C, Stiglitz J. Why inequality could spread COVID-19. Lancet Public Health. 2020; 5(5): e240.

26. Blakey SM, Abramowitz JS. Psychological Predictors of Health Anxiety in Response to the Zika Virus. J Clin Psychol Med Settings. 2017; 24(3-4): 270-8.

27. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated with Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open. 2020; 3(3): e203976.

28. Goulia P, Mantas C, Dimitroula D, Mantis D, Hyphantis T. General hospital staff worries, perceived sufficiency of information and associated psychological distress during the A/H1N1 influenza pandemic. BMC Infect Dis. 2010; 10: 322.

29. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int J Environ Res Public Health. 2020; 17(5): 1729.

30. Franck LS, Spencer C. Informing parents about anaesthesia for children's surgery: a critical literature review. Patient Educ Couns. 2005; 59(2): 117-25.

RESEARCH ARTICLE

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The Relationship Between Asthma/Allergy Symptoms in Children and Indoor Particulate Matter in Schools

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Abstract

BACKGROUND/AIMS: Air pollution is one of the major environmental problems and it is steadily increasing, especially in urban areas. When children start school, they are exposed to airborne pollutants in indoor areas more than outdoor areas. In this study, it was aimed to investigate the relationship between asthma symptoms and indoor particulate matter (PM) measurements and some risk factors in students attending a primary school in Western Türkiye.

MATERIALS AND METHODS: This cross-sectional study was conducted between October and December, 2018. The questionnaire form included questions about the asthma/allergy symptoms of the students, and certain environmental risk factors. Temperature, humidity and PM were measured in the indoor environment of the school.

RESULTS: This study was completed with 412 students and their mean age was 8.66±1.16 years. The two out of ten students had asthma symptoms, allergic rhinitis, or dry cough symptoms, and the prevalence of skin symptoms-eczema was around 4%.

CONCLUSION: The symptoms were related to a family history of asthma and carpets covering more than half of floor area of the home. The symptoms at school were found to be related to an increase in the number of students in the classroom and the PM values.

Keywords: Allergy symptoms, asthma, prevalence, school, indoor, particulate matter, children

INTRODUCTION

Asthma and other atopic diseases, such as allergic rhinitis and eczema, are common health problems affecting children's health. These diseases are seen at higher rates in developed countries compared to developing countries. To determine morbidity and mortality rates, studies determining the prevalence of symptoms related to diseases are valuable.[1,2] Early detection and treatment of allergic symptoms and the identification of risk factors are essential for the prevention of diseases.[2-4] Some of the risk factors may be listed as personal factors, such as age, sex, and immunological status, psychosocial factors, socioeconomic factors, characteristics of the home, and poor indoor air quality in schools, where children spend most of their time.[4-9] The World Health Organization (WHO) reported that 36% of respiratory diseases in children and 22% of chronic diseases are associated with poor indoor air quality in classrooms.[10] Indoor air quality deteriorates with higher temperatures, increased humidity, and the presence of pollutants. Pollutants such as particulate matters (PM), carbon dioxide, high levels of Volatile Organic Compounds, the presence of mold, and passive smoking are known to be associated with increased asthma and allergic symptoms in children.[3,7-9] Especially 0.5 µm diameter PMs enter into the lower airways easily, and close to 60% of $PM_{2.5}$ and PM_{10} are reported to be of external origin.[7-9] Due to building design, ventilation conditions, dynamic activities, and high numbers of students in a limited space, the school indoor environments increase exposure to air pollution.[7] At the same time, it has been stated in epidemiological studies that the exposure of children, who are more sensitive and vulnerable than

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adults, to polluted air in the school environment has negative effects on their neurological development.[3,5,6]

In cross-sectional studies conducted in our country, the prevalence of asthma diagnosed in children aged over six years ranged between 4.8% and 17.6%, while the prevalence of asthma symptoms was reported to be between 6.5% and 17.2%.[11,12] Among these studies evaluating the prevalence of the disease in conjunction with some environmental risk factors, there was no study examining the relationship between indoor PM and symptoms.

In this study, it was aimed to investigate the relationship between asthma symptoms and indoor PM measurements and some risk factors in students attending a primary school in the center of Kütahya in western Türkiye.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted between October and December, 2018. Local ethics committee [Clinical Research Ethics Committee of the Kütahya Health Sciences University (approval number: 2018-13/12)] and institution permissions were obtained for this study. The population of this study consisted of all students studying at a primary school randomly selected from the center of Kütahya.

Procedures

On the designated days, classroom teachers were informed about the study, and questionnaires were distributed to the parents of the students. Verbal and written information was given to the children and the parents about the purpose and scope of this study, and their written consent was obtained. PM measurements were performed in the classrooms on the days following the distribution of the forms. Since participation was voluntary, those children of parents who did not want to answer the questionnaire were excluded from the study. The total number of students studying at the school was 475, and the study was completed with 412 students who agreed to participate (with a participation rate of 86.7%).

Measures

The questionnaire form included questions about the socio-demographic characteristics of the parents, the asthma/allergy symptoms of the students, their history of the physician-diagnosed diseases, and environmental risk factors. There were also questions about the students' gender, their number of siblings, allergic symptoms in school, the smoking status at home, and the conditions in the home. Data related to asthma/allergy symptoms were obtained through "*The International Study of Asthma and Allergies in Childhood-ISAAC*" questionnaire.

The *ISAAC questionnaire* is a form developed by the ISAAC Steering Committee to make comparisons between populations in different countries and to determine the prevalence and severity of asthma, allergic rhinitis, and eczema symptoms in children.[1,2] Many prevalence studies conducted in Türkiye have utilized this form.[11,12] This form investigates whether the children, their parents, or their siblings have had asthma during the last year or throughout their lives and whether they currently have asthma symptoms, allergic rhinitis, or eczema.

The "*Particles Plus 8306 Handheld Particle Counter*" was used at the beginning and end of the lessons for the measurement of the amount of PM away from windows and doors in the classrooms. It was ensured that the doors and windows were closed during the lesson in the classrooms to be measured. While the measurements were made, the devices were calibrated while being transferred from one classroom to another. It is a simple, manual, mobile, sensor-based device which measures temperature, humidity, and PM. This device counts PM values between 0.3 and 25 µm with an airflow rate of 0.1 CFM (2.83 LPM). In this study, we measured indoor air $PM_{2.5}$ (particles less than 2.5 µm in diameter) and PM_{10} (particles less than 10 µm in diameter) values. Measurements can be reported in accordance with ISO 14644-1, E GMP Annex 1, or FS 209. Measurements are given as $\mu g/m^3$.

Definitions

The presence of asthma, asthma symptoms, allergic rhinitis, or eczema in the previous one year was investigated according to the ISAAC form, and those students with any of these in the previous year were defined as the *symptomatic group*.

At the same time, the teachers were interviewed regarding each student in order to determine the severity and frequency of these symptoms while at school. As a result of these interviews, students with symptoms such as coughing, sneezing, runny nose, nasal congestion, itching, watering or reddening of eyes, and redness despite the absence of cold or flu, were defined as the *symptomatic in school group*.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences 27.0 statistical analysis program (IBM SPSS Corp.; Armonk, NY, USA). Qualitative data are given as numbers and percentages and evaluated by the chi-squared test. The means, standard deviations (SD), medians, minimums, and maximums values of the measured data are given. Since the data were not normally distributed, the Mann-Whitney U test was used for the comparison of the group medians, and logistic regression was used for further analysis. In the univariate analysis, two multivariate models were constructed with independent variables with $p<0.10$ values and corrected for age and sex. The *symptomatic group* in the previous year was included as the dependent variable for the first model and the *symptomatic in school group* for the second model. Categorical variables such as the presence of a family history of asthma, the smoking status at home, and carpets covering more than half of the floor area in the home were taken as independent variables for the first model. The presence of a family history of asthma, class size, and PM values measured in the environment (the linear logarithm of some were taken to provide a normal distribution) formed the variables for the second model. The statistical significance was set at $p<0.05$.

RESULTS

This study was carried out in a primary school with 412 students, of whom 47% (n=194) were girls and 52.9% boys (n=218). The mean age of the students in the 1st, 2nd, 3rd, and 4th grades was 8.66±1.16 years (minimum: 7, maximum: 11). Each grade had four classes, and the average size of the classes was 26.7±3.3 students (minimum: 22, maximum: 33).

According to the ISAAC form, the prevalence of asthma, asthma symptoms, allergic rhinitis, dry cough, and eczema, which had been present within the previous one year were 14.1%, 17%, 25.7%, 18.4%, and

4.6%, respectively. The prevalence of previous pneumonia was found to be 5.6%. When the symptoms seen in the school were evaluated, the prevalences were 22.3% for nasal discharge-congestion, 13.1% for dry cough-sneezing, 8.5% for redness-itching-watering of the eyes, and for skin dryness and redness, it was 3.6% (Table 1).

While there was no relationship between the gender and asthma symptoms of the students, the mean age of the symptom group was higher than that of the non-symptom group (Table 2).

Some of the socio-demographic characteristics of the parents and the characteristics of the homes they lived in are presented in Table 3. Table 4 presents the distributions of the means ± SD and minimum-maximum values for class sizes and the measured PM results in the classrooms.

The relationship between the symptomatic in the previous year group and the symptomatic group in terms of the students' risk factors at home and at school, their socio-demographic characteristics, and the measurements were evaluated by univariate analyses. As a result of this analysis, a regression model was created with independent variables giving $p<0.10$ value. These data are presented in Table 5.

According to Model 1, which was established to determine the relationship between asthma and the symptoms of the students seen within the previous year and some risk factors at home; the risk of having asthma was found to be 5.7 times higher ($p<0.001$) for those with a family history of asthma and 2.1 times higher ($p=0.024$) for those who lived in a home with carpets covering more than half of the floor area (Table 5).

According to Model 2, which was established to determine the relationship between asthma and symptoms seen in school and the PM measurements and some other risk factors; the risk of having asthma was found to be 3.5 times higher ($p<0.001$) in those children with a family history of asthma, 1.2 times higher ($p=0.007$) in those with an

Table 1. Distribution of symptoms in students within the previous year generally and at school

The symptomatic group within the previous year	**n**	**%**
Asthma	58	14.1
Asthma symptoms	70	17.0
Allergic rhinitis	106	25.7
Eczema	19	4.6
Pneumonia	23	5.6
Dry cough	76	18.4
The symptomatic in school group	**n**	**%**
No symptoms	216	52.4
Dry cough-sneezing	54	13.1
Runny nose-nasal congestion	92	22.3
Skin redness-itching	15	3.6
Redness-itching-watering of the eyes	35	8.5

Table 2. Comparison of age and gender with symptoms at school

The symptomatic group in the previous year				
	No symptoms (n=216) n (%)	**Symptoms (n=196) n (%)**	**Total (n=412) n (%)**	**Statistics**
Age				
Mean ± SD	8.50±1.09	8.84±1.07	8.66±1.16	t=-2.962 **p=0.003**
Gender				
Male	114 (52.3)	104 (47.7)	218 (52.9)	X^2=0.030
Female	102 (52.6)	92 (47.4)	194 (47.1)	p=0.954
The symptomatic in school group				
	No symptoms (n=347) n (%)	**symptoms (n=65) n (%)**	**Total (n=412) n (%)**	**Statistics**
Age				
Mean ± SD	8.57±1.14	9.14±1.17	8.66±1.16	t=-3.701 **p=0.001**
Gender				
Male	182 (83.5)	104 (16.5)	218 (52.9)	X^2=0.189
Female	165 (85.1)	92 (14.9)	194 (47.1)	p=0.664

SD: Standard deviation.

increased number of students in the classroom, and 1.1 times higher with each step increase of PM_{10} values (Table 5).

The changes in the frequency of the students' symptoms seen at school, according to the measured $PM_{2.5}$ and PM_{10} values are shown in Figure 1, 2. It was found that dry cough-sneezing increased in line with the measured $PM_{2.5}$ values, and redness-itching-irrigation symptoms increased in line with the measured PM_{10} values (Figure 1, 2).

DISCUSSION

Air pollution is one of the major environmental problems and it is steadily increasing, especially in urban areas. Pollution factors in outdoor and indoor air affect health negatively.[4] Children spend most of their lives at school and spend more than 70% of their school time in indoor areas. When children start school, they are exposed to airborne pollutants in indoor areas more than outdoor areas. Classrooms are the second most crucial indoor environment after homes for children.[9] There are PMs of different diameters and sizes in indoor air in classrooms. They are emitted from many sources, such as heating sources, building

Table 3. Socio-demographic characteristics of the students' parents and the homes they live

Socio-demographic characteristics of parents	**n**	**%**
Education of mother (primary school)	196	47.6
Education of father (primary school)	86	20.9
The presence of symptoms (asthma etc.) in the family	85	20.6
Characteristics of the home	n	%
Age of the building (older than 20)	210	51.0
Smoking status at home	143	34.7
House type (detached house)	62	15.0
Floor material (concrete)	82	19.9
Living in a home with carpets covering more than half of the floor area	257	62.4
House heating (stove)	27	6.5
Pets at home	74	17.9
Potted plants at home	193	46.8
Moisture/mold at home	27	6.7

Table 4. Distribution of class size and measurement results

Characteristics of classes, results of the measurements	**Mean ± SD**	**Median**	**Min.-Max.**
$PM_{2.5}$ (μg/m^3)	99.71±18.41	97.49	76.32-143.68
PM_{10} (μg/m^3)	696.98±179.77	682.94	384.23-1187.02
Temperature (°C)	23.22±1.08	23.57	20.1-24.8
Humidity (%)	58.42±5.38	57.24	50.2-70.2
Class size	26.76±3.28	26	22-33

SD: Standard deviation, Min.: Minimum, Max.: Maximum, PM: Particulate matters.

Table 5. The relationship between some of the risk factors and the students' symptoms

	The relationship between some of the risk factors and the students who have seen symptoms within the previous year						
Model 1	**B**	**S.E.**	**Wald**	**p**	**OR**	**95% CI for OR**	
						Lower	**Upper**
The presence of symptoms (asthma etc.) in family	1.737	0.334	27.01	**<0.001**	5.68	2.95	10.33
Smoking status at home	0.632	0.360	3.08	0.079	0.53	0.26	1.07
Living in a home with carpets covering more than half of the floor area	0.746	0.332	5.07	**<0.001**	2.11	1.10	4.04
	The relationship between some risk factors and the group with symptoms at school						
Model 2	**B**	**S.E.**	**Wald**	**p**	**OR**	**95% CI for OR**	
						Lower	**Lower**
The presence of symptoms (asthma etc.) in family	1.264	0.312	16.37	**<0.001**	3.54	1.92	6.52
Class size	0.168	0.062	7.28	**0.007**	1.18	1.05	1.33
$PM_{2.5}$	0.007	0.001	37.06	**<0.001**	1.02	1.01	1.07
PM_{10}	0.010	0.002	39.28	**<0.001**	1.12	1.03	1.21

CI: Confidence interval, OR: Odds ratio, PM: Particulate matters, S.E.: Standard error.

construction materials, ventilation systems, the physical activities of children, and cleaning.[13] Exposure assessment is essential in order to determine the relationship between air pollution and its effects on health. However, one of the biggest challenges of environmental epidemiology is to analyze the nature of this exposure.[14]

We measured indoor air $PM_{2.5}$ and PM_{10} values in a city located in the west of Türkiye, especially on a street which had traffic congestion near schools. In this study, we aimed to evaluate the relationship between PM values and allergic symptoms in children at school and we tried to observe the effects of environmental exposure. At the same time, we also tried to determine risk factors in the home environment, and the prevalence of asthma, asthma-allergy symptoms in the previous year.

In our study, the prevalences of asthma, asthma symptoms, allergic rhinitis, dry cough, or eczema within the previous one year were 14.1%, 17%, 25.7%, 18.4%, and 4.6%, respectively. When the symptoms seen in school were evaluated, 22.3% were nasal discharge-congestion, 13.1% dry cough-sneezing, 8.5% redness-itching-watering in eyes, and 3.6% skin dryness and redness. In another study conducted in our country (Türkiye), similar prevalence values were reported.[11]

In a study of 39,782 children aged 3-6 years in day-care centers in China, the prevalence of doctor-diagnosed asthma was found to be 7.4%, rhinitis was 8.7%, and the prevalences of eczema, wheezing, and rhinitis within the previous one year were 24.1%, 19.7%, and 45%,[4] respectively. The prevalence of doctor-diagnosed asthma in children over six years of age in Nigeria was found to be 3.1%.[15] In another study, it was reported that 29.8% of children had daytime shortness of breath due to the school environment and 8.4% suffered from wheezing.[16] In another study, asthma-like symptoms, nasal allergy, and doctor-diagnosed asthma frequency were found to be higher in boys than in girls in any period of life.[17] In a multicenter study conducted in our country, it was reported that the frequency of symptoms in girls was higher.[11]

In our study, although no relationship was found between the prevalence of symptoms and gender, the mean age of the symptom group was found to be higher.

In addition to personal factors, genetic factors, environmental factors, and socio-economic factors, the poor physical properties of the home were reported to increase asthma and asthma symptoms.[4-9,15]

In support of these data, our study found that the risk of symptoms within the previous year was five times higher for those with a family history of asthma and two times higher for those who lived in homes with carpets covering a large amount of the floor area.

The detrimental health effects of particles vary according to their shape, diameter, and chemical composition. Particularly fine particles, less than 2.5 µm in diameter ($PM_{2.5}$) and less than 1 µm in diameter (PM_1), can cause asthma, allergic rhinitis, and other allergic respiratory diseases. It has been reported that coarse particles (PM_{10}) smaller than 10 µm may cause allergic symptoms such as eye and skin irritations without entering the respiratory system.[13,18] However, a meta-analysis study found that PMs less than 2.5 µg/m^3 may cause skin symptoms such as atopic dermatitis or eczema.[19] In a panel study, it was reported that exposure to $PM_{2.5}$ and PM_{10} accelerates symptoms by changing the nasal microbiota.[20] In a study evaluating the relationship between indoor air quality and the respiratory symptoms of children, it was found that high $PM_{2.5}$ and PM_{10} values increased the risk of wheezing symptoms by 2.3 and 3 times, respectively.[17] In another study, the effect of PM1 and PM_{10} values on asthma symptoms could not be shown, but increased PM_1 values were found to increase the risk of eczema.[21] Moreover, it was shown that as the duration of exposure to these PMs and their concentrations increased, the number of findings also increased.[13,18]

The risk of asthma and asthma symptoms at school was found to be 1.1 times higher with each step increase in $PM_{2.5}$ and PM_{10} levels. However, high $PM_{2.5}$ values were associated with dry cough-sneezing, and high PM_{10} values were associated with redness-itching symptoms in the skin and eyes. Our results support the effects of exposure to fine and coarse particles seen in the literature.

In particular, increased $PM_{2.5}$ and PM_{10} concentrations have been shown to increase atopic diseases and allergic reactions in children in many

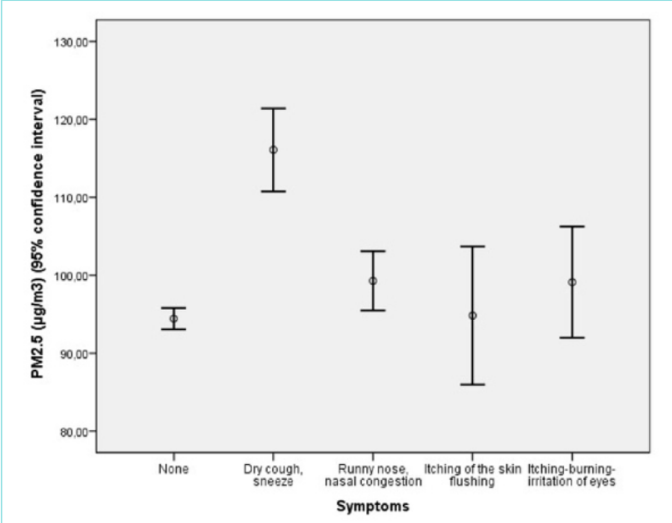

Figure 1. Distribution of students' symptoms in school according to measured $PM_{2.5}$ values.

PM: Particulate matters.

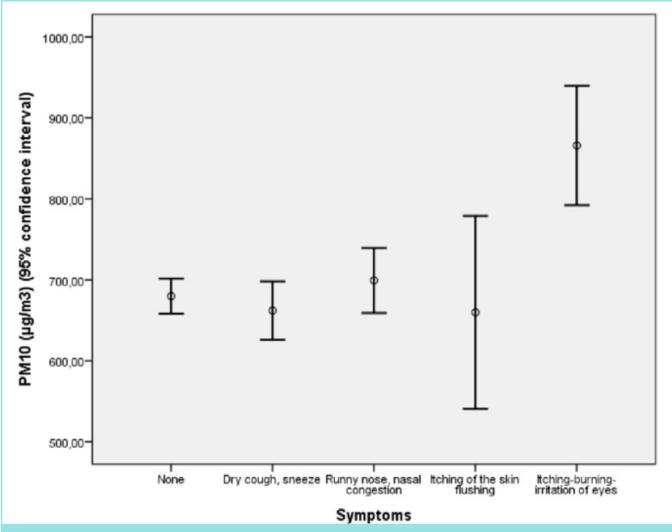

Figure 2. Distribution of students' symptoms in school according to measured PM_{10} values.

PM: Particulate matters.

studies.[13,14,22,23] The WHO has determined the limit values of PM_{10} and $PM_{2.5}$ for indoor air as 50 μg/m^3 and 25 μg/m^3, respectively.[24] When studies measuring the values of $PM_{2.5}$ and PM_{10} indoors in schools were examined, $PM_{2.5}$ and PM_{10} values were found to be higher than the criteria determined by the WHO, as can be seen in a study conducted in Qatar in 16 schools,[25] and by measurements made by Ruggieri et al.[26] in a study in 73 classrooms in 20 schools in Portugal.[27] In China, the $PM_{2.5}$ and PM_{10} values measured in four schools were close to our results.[28]

The mean values of $PM_{2.5}$ and PM_{10} measured in our study were higher than those reported in most other studies. When other studies are examined, it is not correct to make a comparison by considering the measurement values alone. Other factors which may affect the measurement results, such as differences in the season when the measurements were made, the location of the school (distance to the street), the class size, the capacity of the measuring device, the frequency and duration of the measurements, etc. should also be considered.[13,14,16] Furthermore, it should be remembered that close to 60% of $PM_{2.5}$ and PM_{10} in indoor environments originate from the outdoor environment.[7-9]

The fact that we did not carry out our measurements for 24 hours, the high outdoor PM values due to the winter season, and the fact that the classes were more crowded than those reported in other studies, can be put forward as the reasons for the higher measurement results obtained in this study. The risk of asthma and asthma symptoms seen in the school increased by 1.2 times as the number of students in the classroom increased.

Study Limitations

The limitations of this study include the fact that only one questionnaire was applied in one school in an urban area, and that the measurement durations were relatively short. Another limitation is that symptom diagnosis was based on the participants' responses, which might have been affected by memory-related factors. In addition, conducting this study during the autumn/winter season might have affected the results. In our region (Western Türkiye) which has continental climate characteristics, the average daytime temperatures vary between -1 °C and 10 °C during this season. Some of the symptoms may have been due to seasonal viral illnesses. However, since there had been no previous epidemiological studies conducted for this period of the year, the expected rate of viral illnesses is unknown.

CONCLUSION

As a result, approximately two out of ten students had asthma symptoms, allergic rhinitis, or dry cough symptoms, and the prevalence of skin symptoms-eczema was around 4%. The symptoms seen in the previous year were related to a family history of asthma and carpets covering more than half of floor area in the home. On the other hand, the symptoms at school were found to be related to an increased number of students in the classroom and the $PM_{2.5}$ and PM_{10} values.

In this respect, we think that school administrations should be informed in order to make arrangements and take measures to improve the indoor air quality of the school. Adequate ventilation and regular cleaning practices in indoor environments are important at this stage. At the same time, it is essential to eliminate allergen risk factors in the home environment and raise awareness in parents about the continuity of health education. As a next step, studies can be planned in order to determine advanced tests and treatment plans for at risk students.

MAIN POINTS

- When children start school, they are exposed to airborne pollutants in indoor areas more than outdoor areas. There are PMs of different sizes and emitted from many sources in the indoor air in the classroom.
- We measured indoor air $PM_{2.5}$ and PM_{10} values in a city location, especially on a street which had traffic congestion near schools.
- The asthma-allergy symptoms at school were found to be related to an increase in the number of students in the classroom and the PM values measured.
- School administrations should be informed in order to make arrangements and take measures to improve the indoor air quality of the school.

ETHICS

Ethics Committee Approval: Local ethics committee [Clinical Research Ethics Committee of the Kütahya Health Sciences University (approval number: 2018-13/12)] and institution permissions were obtained for this study.

Informed Consent: Verbal and written information was given to the children and the parents about the purpose and scope of this study, and their written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.A., Design: İ.A., Supervision: İ.A., Fundings: İ.A., Ö.F.T., Materials: İ.A., Ö.F.T., Data Collection and/or Processing: İ.A., Ö.F.T., Analysis and/or Interpretation: İ.A., Literature Search: İ.A., Ö.F.T., Writing: İ.A., Critical Review: Ö.F.T.

DISCLOSURES

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

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REFERENCES

1. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998; 351(9111): 1225-32.
2. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J. 1998; 12(2): 315-35.
3. Norbäck D, Lu C, Wang J, Zhang Y, Li B, Zhao Z, et al. Asthma and rhinitis among Chinese children - Indoor and outdoor air pollution and indicators of socioeconomic status (SES). Environ Int. 2018; 115: 1-8.

4. Norbäck D, Lu C, Zhang Y, Li B, Zhao Z, Huang C, et al. Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: Synergistic effects between antibiotics use and PM10 and second hand smoke. Environ Int. 2019; 125: 252-60.
5. Rivas I, Viana M, Moreno T, Pandolfi M, Amato F, Reche C, et al. Child exposure to indoor and outdoor air pollutants in schools in Barcelona, Spain. Environ Int. 2014; 69: 200-12.
6. Mazaheri M, Clifford S, Jayaratne R, Megat Mokhtar MA, Fuoco F, Buonanno G, et al. School children's personal exposure to ultrafine particles in the urban environment. Environ Sci Technol. 2014; 48(1): 113-20.
7. Morawska L, Ayoko GA, Bae GN, Buonanno G, Chao CYH, Clifford S, et al. Airborne particles in indoor environment of homes, schools, offices and aged care facilities: The main routes of exposure. Environ Int. 2017; 108: 75-83.
8. Chen F, Lin Z, Chen R, Norback D, Liu C, Kan H, et al. The effects of PM2.5 on asthmatic and allergic diseases or symptoms in preschool children of six Chinese cities, based on China, Children, Homes and Health (CCHH) project. Environ Pollut. 2018; 232: 329-37.
9. Hou Y, Liu J, Li J. Investigation of Indoor Air Quality in Primary School Classrooms. Procedia Eng. 2015;121:830–7.
10. Who Regional Office for Europe. Health and environment in Europe: progress assessment. WHO Regional Office Europe. 2010. https://www.euro.who.int/__data/assets/pdf_file/0010/96463/E93556.pdf
11. Kurt E, Metintas S, Basyigit I, Bulut I, Coskun E, Dabak S, et al. Prevalence and Risk Factors of Allergies in Turkey (PARFAIT): results of a multicentre cross-sectional study in adults. Eur Respir J. 2009; 33(4): 724-33.
12. Cetemen A, Yenigün A. Aydın il merkezinde okul çocuklarında astım ve allerjik hastalıkların prevalansı. Asthma Allergy Immunol. 2012; 10: 84-92.
13. Dėdelė A, Miškinytė A, Gražulevičienė R. The impact of particulate matter on allergy risk among adults: integrated exposure assessment. Environ Sci Pollut Res Int. 2019; 26(10): 10070-82.
14. Steinle S, Reis S, Sabel CE, Semple S, Twigg MM, Braban CF, et al. Personal exposure monitoring of PM2.5 in indoor and outdoor microenvironments. Sci Total Environ. 2015; 508: 383-94.
15. Ozoh OB, Aderibigbe SA, Ayuk AC, Desalu OO, Oridota OE, Olufemi O, et al. The prevalence of asthma and allergic rhinitis in Nigeria: A nationwide survey among children, adolescents and adults. PLoS One. 2019; 14(9): e0222281.
16. Zhao Z, Zhang Z, Wang Z, Ferm M, Liang Y, Norbäck D. Asthmatic symptoms among pupils in relation to winter indoor and outdoor air pollution in schools in Taiyuan, China. Environ Health Perspect. 2008; 116(1): 90-7.
17. Madureira J, Paciência I, Ramos E, Barros H, Pereira C, Teixeira JP, et al. Children's Health and Indoor Air Quality in Primary Schools and Homes in Portugal-Study Design. J Toxicol Environ Health A. 2015; 78(13-14): 915-30.
18. Chu H, Xin J, Yuan Q, Wang M, Cheng L, Zhang Z, et al. The effects of particulate matters on allergic rhinitis in Nanjing, China. Environ Sci Pollut Res Int. 2019; 26(11): 11452-7.
19. Ngoc LTN, Park D, Lee Y, Lee YC. Systematic Review and Meta-Analysis of Human Skin Diseases Due to Particulate Matter. Int J Environ Res Public Health. 2017; 14(12): 1458.
20. Mariani J, Favero C, Spinazzè A, Cavallo DM, Carugno M, Motta V, et al. Short-term particulate matter exposure influences nasal microbiota in a population of healthy subjects. Environ Res. 2018; 162: 119-26.
21. Chatzidiakou L, Mumovic D, Summerfield AJ, Hong SM, Altamirano-Medina H. A Victorian school and a low carbon designed school: Comparison of indoor air quality, energy performance, and student health. Indoor Built Environ. 2014;23(3):417–32.
22. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Krämer U, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. Am J Respir Crit Care Med. 2008; 177(12): 1331-7.
23. Wang IJ, Tung TH, Tang CS, Zhao ZH. Allergens, air pollutants, and childhood allergic diseases. Int J Hyg Environ Health. 2016; 219(1): 66-71.
24. WHO. Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide; World Health Organization: Geneva, Switzerland, 2006. https://apps.who.int/iris/handle/10665/69477
25. Abdel-Salam MM. Investigation of PM2.5 and carbon dioxide levels in urban homes. J Air Waste Manag Assoc. 2015; 65(8): 930-6.
26. Ruggieri S, Longo V, Perrino C, Canepari S, Drago G, L'Abbate L, et al. Indoor air quality in schools of a highly polluted south Mediterranean area. Indoor Air. 2019; 29(2): 276-90.
27. Wu J, Zhong T, Zhu Y, Ge D, Lin X, Li Q. Effects of particulate matter (PM) on childhood asthma exacerbation and control in Xiamen, China. BMC Pediatr. 2019; 19(1): 194.
28. Peng Z, Deng W, Tenorio R. Investigation of Indoor Air Quality and the Identification of Influential Factors at Primary Schools in the North of China. Sustainability. 2017; 9(7):1180.

RESEARCH ARTICLE

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The Determination of the Corrosion Rates of Rotary Ni-Ti Instruments in Various Irrigation Solutions

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Abstract

BACKGROUND/AIMS: This study's goal was to assess and make a comparison of the electrochemical corrosion rates of nickel-titanium (Ni-Ti) rotary files in cases of their immersion in four various irrigation solutions. Another goal of this research was to investigate and compare the areas of corrosion on the file surface under a scanning electron microscope (SEM).

MATERIALS AND METHODS: The Tafel extrapolation method was employed to perform the electrochemical determination of the corrosion rates of twenty-nine ProTaper Universal Ni-Ti rotary files in 2.5% sodium hypochlorite (NaOCl), 5% NaOCl, 15% ethylenediaminetetraacetic acid (EDTA) and 2% chlorhexidine gluconate (CHX) irrigation solutions (7 files were tested for each irrigant). Data were acquired by utilizing a combined system which contained a voltage scan generator, a potentiostat, and a recorder. In order to find corrosion rates, an extrapolation to corrosion potentials of the linear region of anodic currents acquired from electrochemical current-potential curves was performed. The Kruskal-Wallis One-Way analysis of variance was performed to analyze the data statistically. One randomly selected file from each test group was examined under SEM.

RESULTS: The corrosion rates of Ni-Ti rotary files in the examined solutions under SEM from the maximum to the minimum were as follows: 5% NaOCl >15% EDTA >2.5% NaOCl >2% CHX.

CONCLUSION: The findings of the present research demonstrated that 5% NaOCl, 15% EDTA, and 2.5% NaOCl led to significant corrosion on the surface of the chosen Ni-Ti rotary files.

Keywords: Chlorhexidine gluconate, corrosion, EDTA, Ni-Ti rotary files, sodium hypochlorite

INTRODUCTION

Endodontic treatment involves several instruments used with various irrigation solutions for chemo-mechanical preparation procedures.[1,2] Endodontic files produced from nickel-titanium (Ni-Ti) alloy are commonly utilized for endodontic instrumentation with various cross-sectional shapes, fabrication procedures, and design concepts, improved cutting efficiency, high torsional strength, and flexibility.[2,3] Despite numerous advantages, there is a risk of breakage in the course of root canal instrumentation regarding these files.[4] Ni-Ti endodontic rotary instruments usually fracture through either one or a combination of two mechanisms: torsional stress which is caused by the continuing rotation while the tip of the instrument binds in the canal, and flexural stress (bending stress) which arises by repeated compressive rotation of the instrument.[5] In addition to the repeated stresses on endodontic files, the corrosive environment within the

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root canal may cause instrumental fatigue during chemo-mechanical preparation.[2] Pitting or crevice corrosion affects metallic surfaces negatively and reduces the cutting efficiency of endodontic files, and thus promotes instrument breakage.[1] The corrosion mechanism of endodontic files during chemo-mechanical instrumentation stems from the disinfection and sterilization of the material, the pH, the temperature of the media, or the irrigation procedures.[5-8] Various endodontic irrigants at different concentrations, including NaOCl, citric acid, ethylenediaminetetraacetic acid (EDTA), and chlorhexidine gluconate (CHX), are used as disinfectant agents. Irrigants act as a lubricant during root canal instrumentation and they are necessary for the removal of debris created during usage. They also act as a solvent for tissues, as an agent for the promotion of root canal sterility, and act as a generator of open dentinal tubules on the root canal walls. Despite the numerous benefits of these solutions, the electrochemical and chemical aggressiveness of irrigants on endodontic instruments should also be considered in order to prevent a reduction of the lifespan of instruments with use.[9]

The hypothesis evaluated in this study was that corrosion rates, triggered by contact between metals and different electrochemical activities in the presence of NaOCl, EDTA or CHX may alter the structural integrity of the surface of a ProTaper Universal Ni-Ti file. The current research aimed to assess and make a comparison of the impact of 5% NaOCl, 2.5% NaOCl, 15% EDTA, and 2% CHX solutions on the electrochemical corrosion rates of ProTaper Universal Ni-Ti rotary files, by means of analysis via scanning electron microscope (SEM).

MATERIAL AND METHODS

The testing of twenty-nine new (unused) Ni-Ti rotary endodontic instruments (ProTaper Universal F3 ISO size 25 mm (6% taper), Dentsply Maillefer, Ballaigues, Switzerland) was performed for this research. All files were inspected under a stereomicroscope (S8 APO; Leica, Wetzlar, Germany) for defects and replaced if any defect was detected. In the control group, the instrument were not immersed in irrigation solution (n=1). The instruments were separated into four groups with seven specimens in each group. The irrigation solutions studied were as follows:

1. 2% CHX (pH 6.5) (Drogsan, İstanbul, Türkiye),

2. 5% NaOCl (pH 12.9) (Wizard, RehberKimya, İstanbul, Türkiye),

3. 2.5% NaOCl (pH 9.1) (Wizard, RehberKimya, İstanbul, Türkiye),

4. 15% EDTA (pH 7.5) (Wizard, RehberKimya, İstanbul, Türkiye).

The Tafel extrapolation method was employed for the electrochemical determination of the corrosion rates of the ProTaper Universal Ni-Ti rotary files placed in the irrigation solutions (Figure 1). Electrochemical tests were performed in a three-compartment Pyrex cell at a stable temperature of 37 °C. The cell was water-jacketed, and there was a connection with a constant temperature circulator. ProTaper Universal Ni-Ti rotary files were utilized as experimental electrodes. The files' cutting flutes were placed in the irrigation solutions and allowed to stand for a period of 20 min in the cell before every test in order for the electrode's rest potential to be achieved. A saturated calomel electrode (SCE) was utilized as a reference, while a platinum plate was utilized as a counter electrode. All potentials were referred to the SCE. In the course of the experiments, the continuous mixing of the solutions was carried out by a magnetic stirrer in order to allow for full contact of the solutions being tested with the entire surface of the files.

Data were acquired by utilizing a combined system which contained a voltage scan generator (Wenking VSG 72, Göttingen, Germany), a potentiostat (Wenking LB 75 L, Göttingen, Germany), and a recorder (Yokogawa 3077, Tokyo, Japan). The potential scan rate was selected to be 2.5 mV s^{-1}.

Statistical Analysis

To find the corrosion rates, the extrapolation (Tafel extrapolation) to corrosion potentials of the linear part of anodic currents, acquired from electrochemical current potential curves (E $\log_i$), was performed. Fresh solutions were used for every file. Statistical analysis was conducted with the Kruskal-Wallis One-Way ANOVA. The differences were considered statistically significant when $p<0.001$. One randomly selected file from each test group was kept for surface inspection in a special box to prevent its contact with any other medium at the end of the test. The said files, chosen in a random way, and an unused file (control sample) were examined under SEM and displayed at x250 and x500 magnifications.

RESULTS

Table 1 shows the corrosion rates of ProTaper Universal Ni-Ti instruments in 4 various irrigation solutions. The files' corrosion rates in all of the tested solutions were found to differ statistically significantly ($p<0.001$). The results indicated that the corrosion rates of ProTaper Universal Ni-Ti rotary instruments were at a maximum in the 5% NaOCl solution ($p<0.001$). Among the other solutions, the corrosion rates were revealed to be higher in the 15% EDTA than the 2.5% NaOCl and the 2% CHX ($p<0.001$) solutions. The lowest corrosion rate was determined in the 2% CHX solution.

The SEM microphotographs of the control and the four experimental groups were taken and investigated. In the SEM study on the unused control file, very few defects or debris were found due to the production stage of the file (Figure 2). It was seen that the Ni-Ti file which was

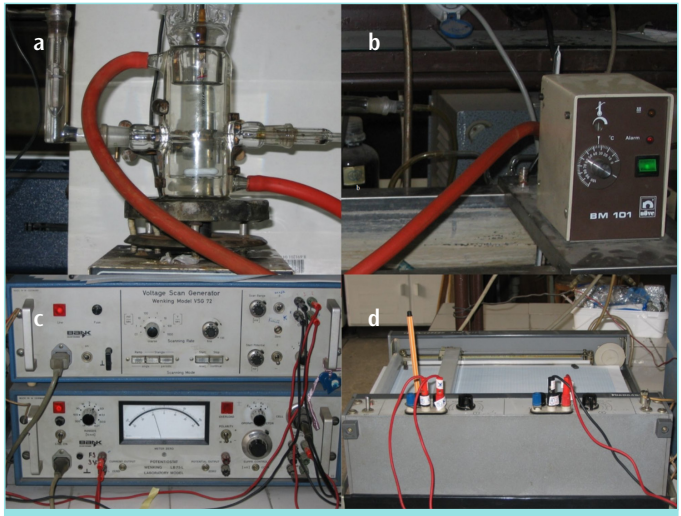

Figure 1. The Tafel extrapolation method. (a) Pyrex glass cell, (b) Thermostat and water motor, (c) Potentiostat and voltage sweep generator, (d) Recorder.

immersed in the 2% CHX solution had corrosion which did not cause a significant change in the surface of the file, and was similar to the control sample (Figure 3). The SEM image of the file in contact with the 2.5% NaOCl solution showed corrosion zones and residual products (Figure 4). Highly dense corrosion zones and residual products which were spread over a large area on the surfaces of files were observed in the SEM images of the instruments immersed in the 5% NaOCl (Figure 5) and 15% EDTA solutions (Figure 6).

DISCUSSION

Endodontic instruments are always subject to stress and corrosive environments in root canal treatment, and during the cleaning and shaping processes in endodontic therapy. The breakage of files while performing the chemical and mechanical debridment of root canals can adversely affect the result of the endodontic treatment. Metal fatigue has been considered as a primary factor in Ni-Ti instrument fracture in clinical conditions.[10] However, the breakage of files should not only be attributed to metal fatigue but also to the negative effects of corrosion on the fracture resistance of files. Metallic surfaces are affected by corrosion which leads to pitting and porosity, which results in the reduced cutting ability of endodontic files. A prolonged use of these files with a reduced cutting ability may increase metal fatigue and the risk of plastic deformation/intracanal separation.[1,10] In this study, the ProTaper Universal Ni-Ti file system, which is widely used for the cleaning and shaping procedures of root canals, was evaluated in terms of its corrosion rate.

Table 1. Corrosion rate (i_{cor}) values of Ni-Ti rotary files in tested solutions

Irrigation solutions	Mean ± SD	Median
2% CHX	0.1214±0.0504	0.12
5% NaOCl	3.150±1.3246	3.25
2.5% NaOCl	0.4529±0.0897	0.45
15% EDTA	2.100±0.2449	2.10

Ni-Ti: Nickel-titanium, SD: Standard deviation, CHX: Chlorhexidine gluconate, NaOCl: Sodium hypochlorite, EDTA: Ethylenediaminetetraacetic acid.

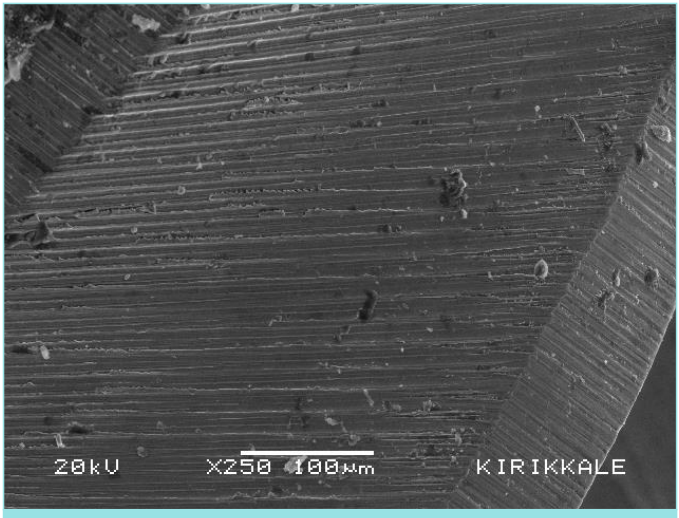

Figure 2. SEM of untreated Ni-Ti control file revealed no evidence of corrosion (x250).

SEM: Scanning electron microscope, Ni-Ti: Nickel-titanium.

Various methods, including atomic force microscopy, the linear polarization method, the alternating current impedance method, open circuit potential and energy dispersive X-ray microanalysis, are used to determine corrosion rates of metals and alloys. In this research, the Tafel extrapolation method was used as an electrochemical test in order to determine the corrosion features of the metals and alloys. Electrochemical techniques which are based on polarization-resistance techniques and polarization profiles are reliable and efficient methods to investigate the corrosion mechanisms of endodontic files. These methods are also used to evaluate the

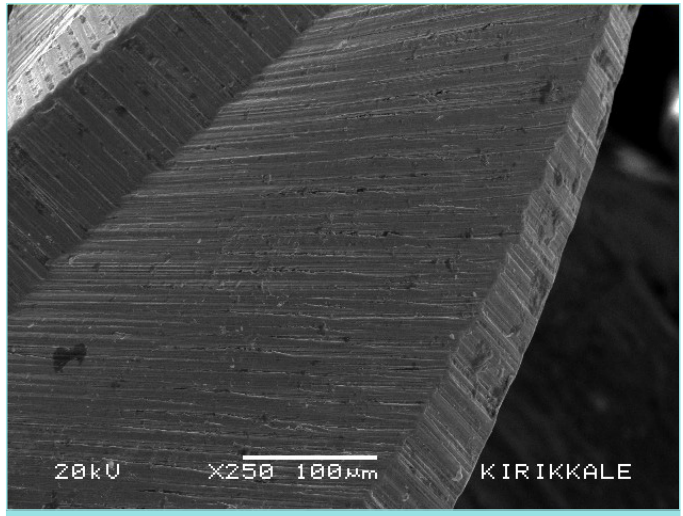

Figure 3. SEM of 2% CHX group revealed the lowest corrosion area (x250).

SEM: Scanning electron microscope, CHX: Chlorhexidine gluconate.

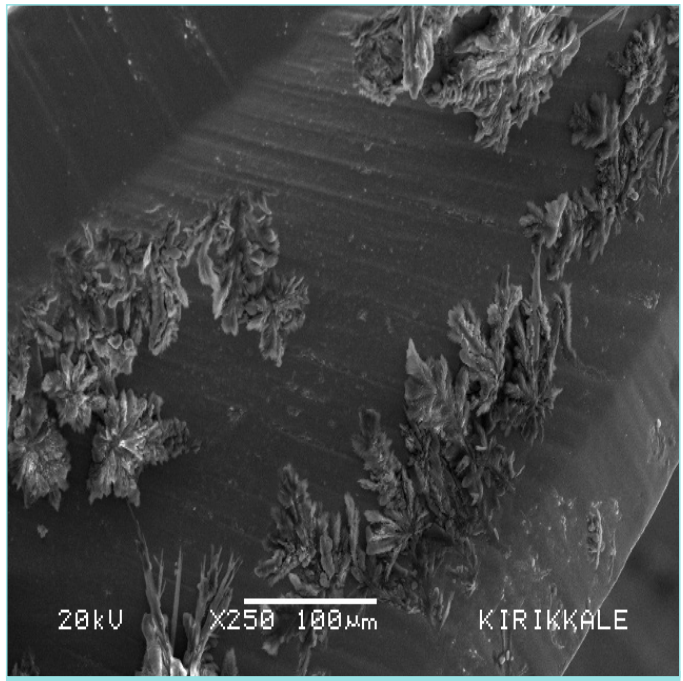

Figure 4. SEM observed that corrosion occurred in local regions in 2.5% NaOCl group (x250).

SEM: Scanning electron microscope, NaOCl: Sodium hypochlorite.

corrosion sensitivity of recently created and enhanced materials for the production of instruments.[1,8,9]

In the present study, the corrosion rates of Ni-Ti instruments in four various irrigants from the strongest to the mildest were as follows: 5% NaOCl >15% EDTA >2.5% NaOCl >2% CHX. These results are likely to be related to active Cl^- which is an important aggressive ion which usually causes increased corrosion rates as NaOCl contains active chloride (Cl^-) ions.[11] The corrosion rate was lowest in the CHX group, which can be explained by the fact that CHX does not contain active Cl^- ions.

Complexes are formed by EDTA with metal ions (e.g., Co, Cr, Fe, Ni, etc.) at low pH (<4).[6] The capability of EDTA to passivate and ensure the protection of instruments is explained by its capability to form complexes with iron in order to create an inhibiting barrier to oxidation and corrosion.[12,13] Furthermore, it is very difficult for the large molecules of EDTA to concentrate and orient to the pit in order to increase the acidity to sufficient values for the purpose of triggering corrosion.[14] However, EDTA easily forms Ni-Ti complex in the range of pH 5.0-8.0, and this complex dissolves abundantly in polar solvents so that the dissolution of the complex leads to an increase in the corrosion rate.[15] Hence, 15% EDTA was found to have the second highest corrosion rate following 5% NaOCl solution, and its corrosion layer was seen to be diffused throughout the entire surface of the file in this research.

The corrosion rate of the 2.5% NaOCl group was lower than that of the 5% NaOCl group due to the decreased the amount of active Cl^- ions by concentration. O'Hoy et al.[8] found that Milton's solution (19% NaCl + 1% NaOCl) was more corrosive than a 1% NaOCl solution. Since 2.5% NaOCl solution exhibited less corrosion on the surface of the files, it may be safer to use it as an irrigant while using rotary Ni-Ti files.

Darabara et al.[16] found that H-files manufactured from two various stainless steel alloys and one file manufactured from Ni-Ti alloy were not susceptible to pitting or crevice corrosion in NaOCl and R-EDTA solutions. In contrast with our findings, they showed that all materials demonstrated higher corrosion potential in NaOCl compared with R-EDTA. Cavalleri et al.[17] also reported that contact with NaOCl for up to 10 minutes does not alter the surface of ProTaper Universal files through corrosion. This result may be attributed to the difference in their analysis method from ours. However, Dartar et al.[9] compared the corrosion rates of stainless steel endodontic files placed in various irrigation solutions and found that 0.2% CHX, 5.25% NaOCl and chlorinated soda with potassium hydroxide led to significant corrosion on the surface of the chosen stainless steel files. The lowest corrosion rate of stainless steel files was seen in 17% EDTA solution.[8] Yum et al.[18] compared the corrosion tendency of used and unused ProTaper Universal Ni-Ti files and different immersion temperatures of NaOCl. They demonstrated that the solution temperature and the chloride ion concentration had an effect on the passivity and corrosion resistance of Ni-Ti files after clinical use. Anto et al.[19] concluded that 2.5%, 5.25% and 8.25% NaOCl caused a deterioration on the ProTaper Universal Ni-Ti files surface. In our study, we also demonstrated that NaOCl at higher concentrations caused highly dense corrosion zones on the Ni-Ti file surface. In accordance with our findings, Sağlam et al.[20] found that 2% chlorhexidine demonstrated limited surface alterations on ProTaper Universal Ni-Ti files when compared to the 2.5% NaOCl, 5% NaOCl and a mixture of tetracycline, citric acid, and detergent (MTAD). Several studies also observed localized corrosion defects

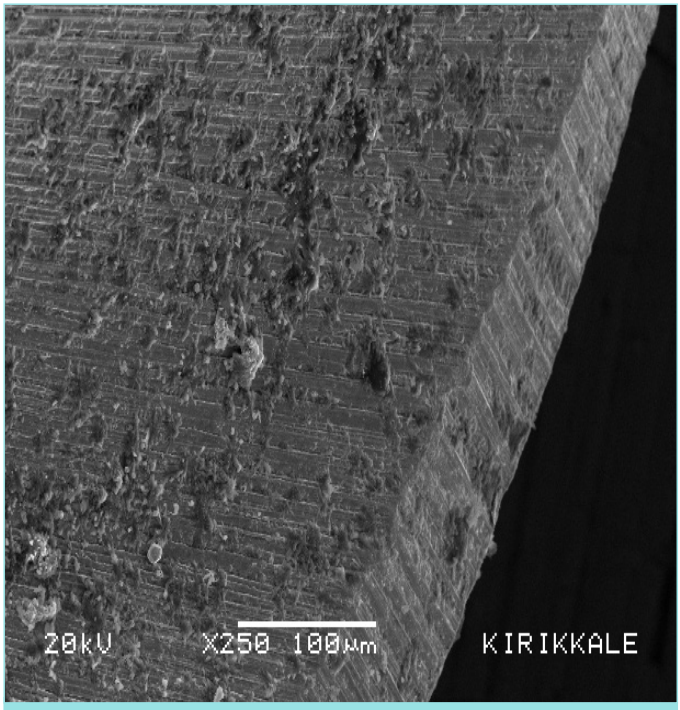

Figure 5. SEM images of a compact and complex corrosion layer on files which were immersed in 5% NaOCl (x250).

SEM: Scanning electron microscope, NaOCl: Sodium hypochlorite.

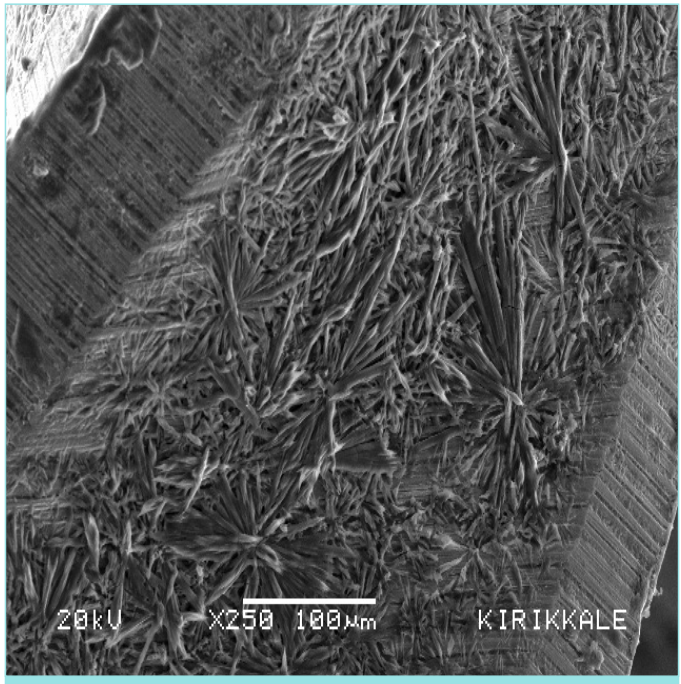

Figure 6. SEM images of a compact and complex corrosion layer on files which were immersed in 15% EDTA (x250).

SEM: Scanning electron microscope, EDTA: Ethylenediaminetetraacetic acid.

and micro-cracks on the surfaces of ProTaper Universal Ni-Ti files after immersion in 2.5 and 5% NaOCl solution.[2,6,9,16]

Berutti et al.[21] showed the presence of localized corrosion attack on the surface of ProTaper Ni-Ti files which were immersed in 5% NaOCl via SEM images. In our study, large corroded areas on the surfaces of ProTaper Ni-Ti files immersed in 5% NaOCl solution were observed in SEM images. Cassol et al.[22] also noted uniform corrosion areas on ProTaper Universal and WaveOne Gold Ni-Ti files which were immersed in NaOCl via SEM imaging.

Study Limitations

The major limitation of the present study was that it was only carried out with Protaper Universal Ni-Ti files, whereas numerous different types of file systems have been introduced to the dental market over the previous few years. Manufacturers are increasingly trying to develop improved Ni-Ti rotary instruments aimed at providing better mechanical and metallurgical properties, enhanced cutting efficiency, fatigue resistance, and corrosion resistance. Cryogenic treatment, thermal nitridation, ion implantation and electro-polishing are a few examples of the strategies used to create enhanced instrument surfaces. There is no doubt that different instruments manufactured in different methods can have different properties in terms of their corrosion resistance. Future studies on the current topic are therefore recommended in order to reveal the corrosion behaviors of newly developed Ni-Ti rotary instruments. Similarly, in future investigations, it would be interesting to conduct research with different types of newly developed endodontic irrigants in order to disclose their corrosion potentials on endodontic instruments. One of the other limitations of the present study was that the *in vitro* conditions may not reflect the *in vivo* conditions accurately since dentin has considerable buffering capacity against irrigants. Therefore, further studies should be conducted in order to evaluate the corrosion rates of root canal irrigants during root canal treatment procedures with Ni-Ti rotary files under *in vivo* conditions.

CONCLUSION

Understanding the corrosion characteristics of endodontic files in various irrigation solutions is essential because of the corrosion tendencies of files in the course of root canal preparation may cause instrument fractures, which are unpleasant accidents. In conclusion, clinicians should be aware of defects which may form on files and the optimal number of uses of each root canal instrument in order to reduce the risk of instrument fracture. In terms of the tested solutions in the present study, the least damaging and the safest irrigation solution for these instruments is CHX.

MAIN POINTS

- The average corrosion rates of the files in the four various irrigation solutions tested are as follows: 5% NaOCl >15% EDTA >2.5% NaOCl >2% CHX.
- According to the corrosion rates determined, the rate of corrosion increases as the concentration of NaOCl solution increases.
- In the SEM investigation, highly dense corrosion zones and corrosion residual products were found on the surfaces of the file selected from the 5% NaOCl solution group.
- The 2% CHX solution used in our study had the lowest average corrosion rate on Ni-Ti rotary files. The corrosive effect of this solution on nickel-titanium files is minimal and so was preferential, as determined via the SEM images obtained.
- The average corrosion rates determined by the Tafel extrapolation method in the four various irrigation solutions used were supported by the SEM findings.

ETHICS

Ethics Committee Approval: Ethics committee approval was not required.

Informed Consent: Informed consent approval was not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.Ö., B.S., M.D.Ö., F.B., U.A., Design: T.Ö., B.S., M.D.Ö., Supervision: T.Ö., B.S., M.D.Ö., Fundings: T.Ö., B.S., M.D.Ö., Materials: T.Ö., B.S., M.D.Ö., F.B., U.A., Data Collection and/or Processing: T.Ö., B.S., F.B., U.A., Analysis and/or Interpretation: T.Ö., B.S., F.B., U.A., Literature Search: F.B., U.A., Writing: F.B., U.A., Critical Review: F.B., U.A.

DISCLOSURES

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REFERENCES

1. Mohammadi Z, Kinoshita JI, Manabe A, Kobayashi M, Shalavi S, Jafarzadeh H. Corrosion of Ni-Ti rotary instruments: a review. J Dent Mater Tech. 2019; 8(4): 215-9.
2. Stokes OW, Fiore PM, Barss JT, Koerber A, Gilbert JL, Lautenschlager EP. Corrosion in stainless-steel and nickel-titanium files. J Endod. 1999; 25(1): 17-20.
3. Hasegawa Y, Goto S, Ogura H. Effect of EDTA solution on corrosion fatigue of Ni-Ti files with different shapes. Dent Mater J. 2014; 33(3): 415-21.
4. Walia HM, Brantley WA, Gerstein H. An initial investigation of the bending and torsional properties of Nitinol root canal files. J Endod. 1988; 14(7): 346-51.
5. Spili P, Parashos P, Messer HH. The impact of instrument fracture on outcome of endodontic treatment. J Endod. 2005; 31(12): 845-50.
6. Nóvoa XR, Martin-Biedma B, Varela-Patiño P, Collazo A, Macías-Luaces A, Cantatore G, et al. The corrosion of nickel-titanium rotary endodontic instruments in sodium hypochlorite. Int Endod J. 2007; 40(1): 36-44.
7. Bayramoğlu G, Alemdaroğlu T, Kedici S, Aksüt AA. The effect of pH on the corrosion of dental metal alloys. J Oral Rehabil. 2000; 27(7): 563-75.
8. O'Hoy PY, Messer HH, Palamara JE. The effect of cleaning procedures on fracture properties and corrosion of NiTi files. Int Endod J. 2003; 36(11): 724-32.
9. Dartar Oztan M, Akman AA, Zaimoglu L, Bilgiç S. Corrosion rates of stainless-steel files in different irrigating solutions. Int Endod J. 2002; 35(8): 655-9.
10. Mueller HJ. Corrosion determination techniques applied to endodontic instruments - irrigating solutions systems. J Endod. 1982; 8(6): 246-52.

11. Gambarini G. Cyclic fatigue of nickel-titanium rotary instruments after clinical use with low- and high-torque endodontic motors. J Endod. 2001; 27(12): 772-4.

12. Katayama H, Yamamoto M, Kodama T. Degradation behavior of protective rust layer in chloride solution. Zairyo-to-Kankyo 2000; 49: 41-4. https://www.jstage.jst.go.jp/article/jcorr1991/49/1/49_1_41/_article/-char/ja/

13. Reinhard G, Radtke M, Rammelt U. On the role of the salts of weak acids in the chemical passivation of iron and steel in aqueous solutions. Corros Sci. 1992; 33(2): 307-13.

14. Skoog DA, West DM, Holler FJ. Fundamentals of analytical chemistry. Saunders, 1992. https://www.academia.edu/43095131/Fundamentals_of_Analytical_Chemistry_9th_Edition

15. Skoog DA, West DM, Holler FJ, Crouch SR. Complexation and precipitation reactions and titrations. Fundamentals of Analytical Chemistry. 9 th. ed. Books/Cole Cengage Learning Chapter 17. 2013; 400-40. https://drive.uqu.edu.sa/_/ajalzahrani/files/Fundamentals%20Of%20Analytical%20Chemistry.pdf

16. Darabara M, Bourithis L, Zinelis S, Papadimitriou GD. Susceptibility to localized corrosion of stainless steel and NiTi endodontic instruments in irrigating solutions. Int Endod J. 2004; 37(10): 705-10.

17. Cavalleri G, Cantatore G, Costa A, Grillenzoni M, Comin Chiaramonti L, Gerosa R. The corrosive effects of sodium hypochlorite on nickel-titanium endodontic instruments: assessment by digital scanning microscope. Minerva Stomatol. 2009; 58(5): 225-31.

18. Yum JW, Park JK, Hur B, Kim HC. Comparative analysis of various corrosive environmental conditions for NiTi rotary files. J Kor Acad Cons Dent. 2008; 33(4): 377-88.

19. Anto T, Anil A, George L, Dhanapal P, Charlie KM, Paul S. Evaluation of the effect of various concentration of sodium hypochlorite on the surface roughness of Protaper rotary files using atomic force microscopy: an in vitro study. Cons Dent Endod J. 2018; 3(2): 56-61.

20. Sağlam BC, Koçak S, Koçak MM, Topuz O. Effects of irrigation solutions on the surface of ProTaper instruments: a microscopy study. Microsc Res Tech. 2012; 75(11): 1534-8.

21. Berutti E, Angelini E, Rigolone M, Migliaretti G, Pasqualini D. Influence of sodium hypochlorite on fracture properties and corrosion of ProTaper Rotary instruments. Int Endod J. 2006; 39(9): 693-9.

22. Cassol LG, Kowalczuck A, Carneiro E, Westphalen VPD, Laurindo CAH, da Silva Neto UX. Evaluation of fluoride and sodium hypochlorite solutions during the electrochemical dissolution of conventional NiTi instruments and Gold thermomechanically treated NiTi instruments. Int Endod J. 2020; 53(4): 513-8.

RESEARCH ARTICLE

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Inactive Platelet Rich Plasma in Culture Conditions Increases the Proliferation and Decreases the Apoptosis and Senescence of Human Adipose Derived Mesenchymal Stem Cells

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Abstract

BACKGROUND/AIMS: The aim of this study was to evaluate the effects of 10% platelet rich plasma (PRP) on the biological activity of human adipose-derived mesenchymal stem cells (hADSCs).

MATERIALS AND METHODS: hADSCs were obtained from Erciyes University Gevher Nesibe Genom and Stem Cell Institute. The cells were transferred into plates at a density of 5,000 cells/cm^2 in DMEM supplemented with 10% fetal bovine serum. Immunophenotyping was performed by means of primary antibodies selected against CD44, CD90, CD105, CD34, CD45 and CD73 antigens. The experimental groups were composed of 10% PRP treated cells (the *study group*) and untreated cells (the *study group*). 2,5-diphenyltetrazolium bromidetest was performed to demonstrate proliferation. Viability and apoptosis were evaluated in the experimental groups on days 1, 3 and 7. Senescent cells were determined by β-galactosidase staining in the experimental groups on day 7.

RESULTS: hADSCs were positive for the immunophenotype of mesenchymal stem cells. The viability and proliferation parameters were statistically significant and higher in the *study group* at days 1, 3 and 7. Apoptosis and senescence were lower in the 10% PRP group ($p<0.05$).

CONCLUSION: 10% PRP increases proliferation and viability, and prevents the senescence and total apoptosis in hADSCs. In regenerative medical studies, 10% PRP can be used to increase the biological characteristics of hADSCs.

Keywords: Platelet rich plasma, adipose-derived mesenchymal stem cell, apoptosis, proliferation, cellular senescence

INTRODUCTION

Stem cells are the main cells which can proliferate, self-renew and differentiate. One of the stem cells in adult tissues are mesenchymal stem cells (MSCs). Bone marrow, adipose tissue, synovial fluid, umbilical cord and dental pulp are important sources of MSCs.[1] MSCs express a high level of surface markers such as CD44, CD73, CD90 and CD105. Under appropriate conditions, they are differentiated into adiogenic, osteogenic and chondrogenic cell lines. Therefore, they are multipotent stem cells.[2] Adipose tissue is one of the richest sources of MSCs. The stem cells obtained here are anti-inflammatory and exhibit multi-lineage differentiation properties very well.[3] Adipose-derived stem cells (ADSCs) are similar to other MSCs in terms of their regenerative potential.[4] In terms of orthopedics, regenerative medicine and tissue engineering, platelet rich plasma (PRP) is an important biological material which contains plenty of growth factors. Recently, it has been used as a cell scaffold.[5] PRP is also an autologous biological product which can be

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used in existing cellular and regenerative medicine treatments. PRP induces proliferation and differentiation of MSCs. As it can be used alone, the use of stem cells together may increase the effectiveness of treatment.[6] PRP refers to the plasma in which the platelet concentration is increased. Platelets contain key factors in key pathways such as vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β). Increases in platelet concentration provide more growth factors to the environment. These factors play a role as a potent potentiator in cells.[7] The purpose of this study was to evaluate the effects of 10% non-activated PRP on the biological activities of human adipose-derived mesenchymal stem cells (hADSCs) such as viability, apoptosis, proliferation and senescence.

MATERIALS AND METHODS

Culture and Characterization of hADSCs

hADSCs were obtained from the Erciyes University Genom and Stem Cell Center. The cells were thawed rapidly in a 37-degree water bath and were transferred onto plates at a density of 5,000 cells/cm^2 in DMEM (Gibco, USA) supplemented with 10% fetal bovine serum (FBS) (Biological Industries, Beit-Haemek, Israel). Phenotyping was carried out by flow cytometry antibodies specific for CD markers (CD34, CD45, CD73, CD90, CD44, and CD105) and analyzed by flow cytometry Navios (BeckmanCoulter, USA). The cells were first gated on the basis of light-scatter properties to screen out debris and cell surface phenotypes were verified via antibodies. The data were analyzed with KALUZA software (BeckmanCoulter, USA). More than 50% staining was regarded as positive. In addition, immunocytochemistry was performed for CD44, CD105 and CD34 markers (BD Bioscience, Heidelberg, Germany).

Preparation of PRP

PRP was isolated from a healthy donor with an optimized method using a PROSYS PRP Kit. Approximately 20 mL of venous blood was collected and centrifuged by means of a blood cell separation kit (PROSYS PRP). After separating the platelet poor plasma formed on the kit, a PRP was injected. The resulting PRP was brought to optimum pH with 8.4% sodium bicarbonate and applied at a 10% concentration to the experimental groups. After a third passage, the cells were treated with 10% PRP (the *study group*) and they were seeded into 6-well plates (3x10^4/well). Those cells without treatment served as the *control group*.

MTT Proliferation Assay

For the proliferation of the *control* and the *study groups*, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was conducted. The cells were seeded at 5,000 cells/cm^2 in a 96-well plate in a standard culture condition. Every day for 7 days of culturing, the culture medium was replaced with 500 µg/mL MTT in medium. Following 4 hours of incubation, the MTT solution was removed and dimethylsulfoxide was added to dissolve the formazan. The absorbance was measured at a wavelength of 560-750 nm with a Glomax Multi Detection System microplate reader (Promega, USA).

Cell Viability Assay

Viability percentages of the cells in the *control* and *study groups* were determined according to the product protocol with the Muse Cell Analyzer (Merck Millipore) cell count and viability kit (Muse Count & Viability Kit MCH100102) on the first, third and seventh days.

Apoptosis (Annexin V) Assay

Rates of total apoptosis in the *control* and *study groups* were determined according to the product procedure by fluorescence-labeled Annexin V using Muse EasyCyte flow cytometry on the first, third and seventh days (Muse EasyCyte, Merck Millipore, Germany).

Senescence-Associated Beta-Galactosidase Assay

X-gal staining for β-galactosidase activity was performed on the *control* and *study groups* on the seventh day. The samples were rinsed twice with PBS and fixed in 2.5% glutaraldehyde for 15 minutes. The cells were washed with PBS, and then stained overnight at 37 °C in X-gal solution with a pH of 6.0 containing 1 mg/mL X-gal (Sigma-Aldric, US.), 5 mM potassium ferricyanide, 5 mM potassium ferrocyanide, and 2 mM $MgCl_2$. X-gal positive cells were examined under an inverted microscope (Nikon Eclipse-Ti, Netherlands).

Statistical Analysis

Statistical analyses were performed using the GraphPad Prism version 6.00 for Windows (GraphPad Software, San Diego California USA). A two tailed, unpaired Student's t-test was applied to analyze the difference between the average responses of the *control* and *study groups*. Three levels of significance were considered: $^*p<0.05$, $^{**}p<0.01$, and $^{***}p<0.001$.

RESULTS

hADSCs Positively Expressed the MSC Markers

hADSCs were expanded in DMEM supplemented with 10% FBS (Figure 1). At the end of passage 3, the phenotype characterization of the hADSCs demonstrated a homogeneous population of cells negative for CD34, CD45 and positive for CD44, CD73, CD90, and CD105 (Figure 2). In addition, the results of immunoflorescent stain showed positive for CD44 and CD105 and negative for CD45 (Figure 3).

PRP Increased the Proliferation of hADSCs

According to MTT assay results, proliferations were statistically significant and higher in the *study groups* at all times (on day 1: p=0.0002, on day 2: p<0.0001, on day 3: p<0.0001, on day 4: p<0.0001, on day 5: p<0.0001, on day 6: p<0.0001, on day 7: p=0.0037) (Figure 4).

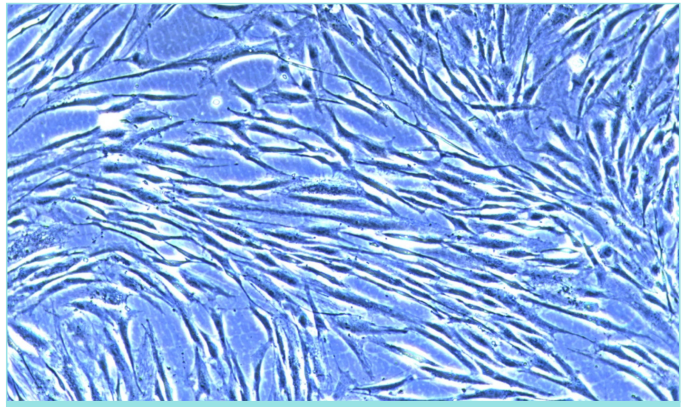

Figure 1. The morphology of hADSCs in culture. Passage 3, microscope magnification 10x.

hADSCs: Human adipose-derived mesenchymal stem cells.

Viability Assay

At the end of the viability tests performed by using the Muse® Cell Analyzer count and viability, first day viability was found to be 91.2±1.39% in the *control group* and 95.76±0.71% in the *study group* (p=0.0833). Third day viability was found to be 91.55±1.14% in the *control group* and 95.15±0.92% in the *study group* (*p*=0.1628). Seventh day viability was found to be 82±0.87% in the *control group* and 86.23±1.65% in the *study group* (*p*=0.1042). There was no statistically significant difference, although there was some increase in viability on days 1, 3 and 7 in the *study group* (Figure 5).

PRP Decreased the Apoptosis of hADSCs

At the end of apoptosis tests performed by using the Muse® Cell Analyzer Annexin V, first day total apoptosis was found to be 8.05±1.48% in the *control group* and 3.21±0.45% in the *study group* (p=0.0071). Third day total apoptosis was found to be 7.5±1.13% in the *control group* and 3.18±0.98% in the *study group* (p=0.0108). Seventh day total apoptosis was found to be 14.95±0.45% in the *control group* and 3.23±0.43% in the *study group* (p=0.0002) (Figure 6).

Senescence-Associated Beta-Galactosidase Assay

Senescence were statistically significant and lower in the *study group* (p<0.05) (Figure 7). PRP decreased the cellular senescence of hADSCs. The number of beta-galactosidase positive cells were found to be 93±5.86 in the *control group* and 14±3.18 in the *study group* (p=0.0003).

DISCUSSION

PRP is a blood plasma containing a high platelet concentration. Platelets contain large amounts of natural growth factors. The concentration of circulating platelets in one microliter is 200,000, while the concentration of platelets in PRP is over two million per microliter.[5] Platelets contain growth factors which regulate many processes associated with healing and tissue repair at high concentrations.[6] These processes include cell migration, proliferation, angiogenesis, inflammation mediator and collagen synthesis.[7] PRP is an important tool used in orthopedic surgery and regenerative medicine. PRP, which can also be administered allogeneically due to the immunosuppressive properties of MSCs, contains TGF-β1, BMP2, platelet-derived growth factors, VEGF and many other factors. Another study previously performed by us showed that it improves the potentials of MSCs of TGF-β1 overexpression.[8] PRP is

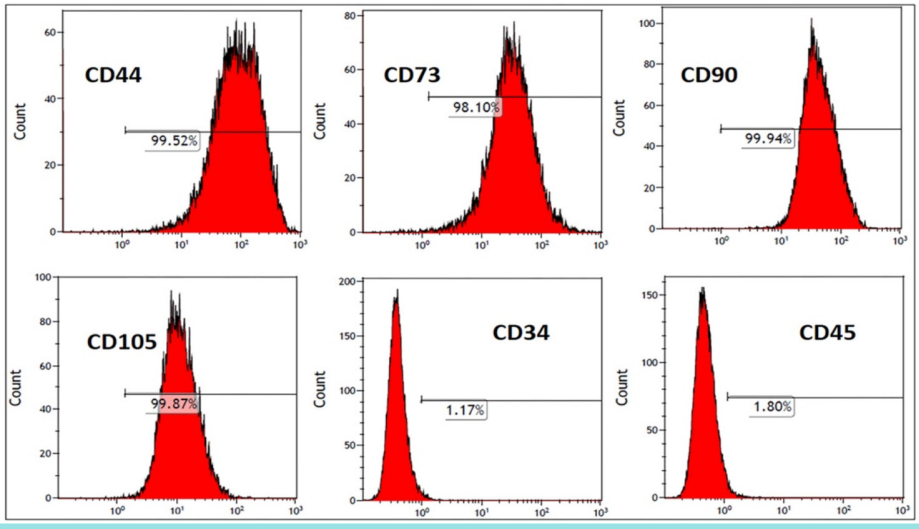

Figure 2. Analyses of flow cytometry for hADSCs. The results of flow cytometry show the following: 99.52% of CD44, 98.10% of CD73, 99.94% of CD90, 99.87% CD105, 1.17% of CD34 and 1.80% of CD45.

hADSCs: Human adipose-derived mesenchymal stem cells.

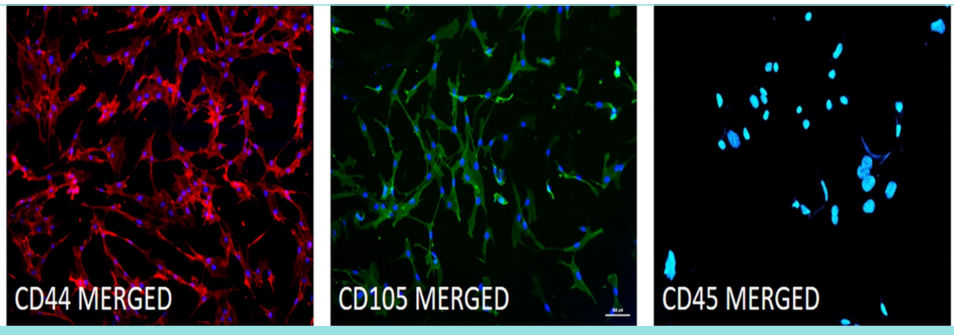

Figure 3. The immunocytochemistry of hADSCs. CD44 positive, Texas Red, CD105 positive, FITC and CD45 negative, FITC. Microscope magnification is 20x for the CD44 and CD105 merged images, and it is 40x for the CD45 merged image.

hADSCs: Human adipose-derived mesenchymal stem cells.

a biological source which is rich in growth factor TGF-β1 and it can be used in studies such as cellular therapy, tissue engineering and regenerative medicine to improve the biological potential of cells. In our study, we employed PRP at 10% concentration, with the aim of determining if PRP could stimulate the proliferation of hADSCs. There are several stem cell studies in the literature with various percentages for PRP applications. Lucarelli et al.[9] found that PRP was an inducer at 10% concentration for the proliferation of marked bone marrow cells. Other investigations have also shown the effects of PRP on the proliferation of MSC.[10,11] The effects of PRP on the proliferation and differentiation of bone marrow-derived MSCs were assessed in 2005 by Doucet et al.[12]. Lee et al.[13] investigated the effects of PRP obtained from human umbilical cord blood on the proliferation and osteogenic differentiation of dental stem cells.Various concentrations of PRP were tried and found to induce the proliferation and osteogenic differentiation of dental stem cells. Stessuk et al.[14] reported that 10% PRP increased the proliferation of keratinocytes and fibroblasts and that wound healing and chronic wounds could achieve re-epithelization with ADSC and PRP. In 2015, Seyhan et al.[15] reported that the combination of PRP + ADSC reduced fat resorption and improved fat grafts in adipose tissue transplantations. Also, Shen et al.[16] reported that autologous PRP application enhanced the proliferation and chondrogenic differentiation of ADSCs. At the same time, the success of the implantation of ADSC with PRP in human articular joints was reported in the literature by Pak et al.[17]. Activated PRP has been proposed as a 3D scaffold and as being effective in the repair of articular cartilage damage with ADSCs.[18] PRP increases angiogenic and osteogenic differentiation, induces cartilage regeneration, and is used as a scaffold in tissue engineering.[19-21] In the literature, the effects of PRP on the proliferation and differentiation of ADSCs have been evaluated in general, but its effects on biological mechanisms such as apoptosis and senescence have not been investigated in detail. In our study, the effects of PRP were evaluated on proliferation, viability, apoptosis and senescence in hADSCs. Our findings showed that PRP significantly increases proliferation in hADSCs, reducing total apoptosis and senescence. In 2017, Felthaus et al.[22] reported that PRP concentrations above 20% showed an inhibitory effect on ADSCs.

CONCLUSION

As a result of this, a 10% PRP concentration was preferred in our study. Using a biological, readily available, inexpensive and reliable source, such as PRP, which naturally contains many of these factors in its own right, instead of giving exogenous recombinant proteins or growth factors for the proliferation and differentiation of cells, can greatly enhance the potential of stem cells. Thus, PRP may be used safely on hADSCs.

MAIN POINTS

- 10% PRP increases the vitality of ADSCs.
- 10% PRP increases the proliferation of ADSCs.
- Inactive PRP application reduces apoptosis in ADSCs.
- Inactive PRP application reduces cellular senescence in ADSCs.
- 10% inactive PRP can be used safely to strengthen the biological characteristics and therapeutic effects of ADSCs.

Acknowledgements: This study and its abstract were presented as a poster for the 2nd International Stem Cell Congress, 15-18 October, 2015 in Antalya, Türkiye and was published as an abstract in the congress book.

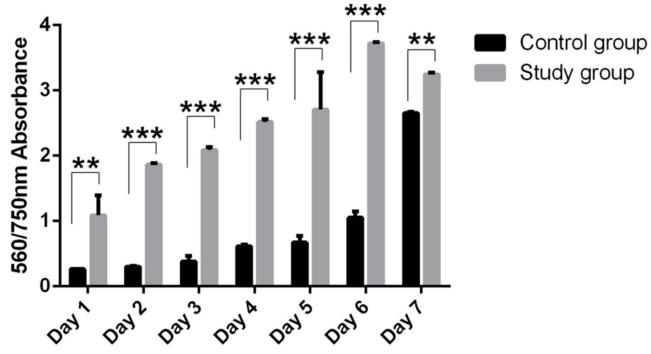

Figure 4. The results of MTT measurements show induced proliferation at 7 days of 10% PRP in hADSCs.

MTT: 2,5-diphenyltetrazolium bromide, PRP: Platelet rich plasma, hADSCs: Human adipose-derived mesenchymal stem cells.

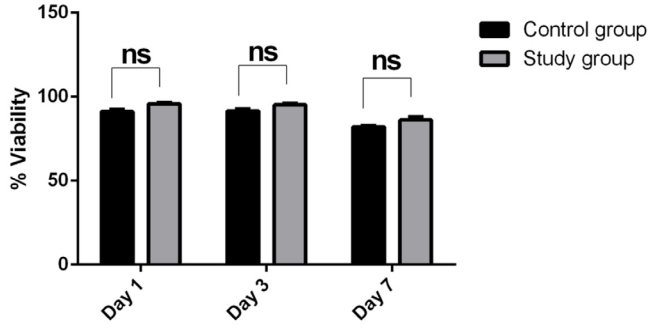

Figure 5. Muse Count and Viability (Millipore, USA) test. There was no statistically significant difference, although there was some increase in viability on days 1, 3 and 7 in the *study group*.

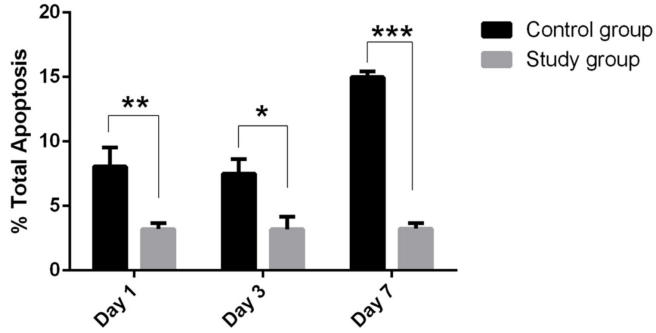

Figure 6. Total apoptosis percentages are shown. According to these results, the total apoptosis in the first, third and seventh days decreased significantly in the *study group*.

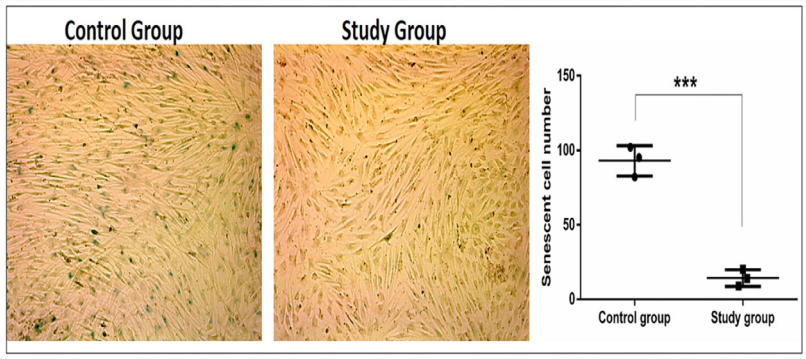

Figure 7. β-galactosidase staining on the 7th day after PRP treatment.
PRP: Platelet rich plasma.

ETHICS

Ethics Committee Approval: Since human adipose-derived stem cells were obtained from Erciyes University Genome and Stem Cell Center as a ready-made commercial cell line in our study, an ethics committee document was not needed.

Informed Consent: Cells were obtained as commercial cell line, not human.

Peer-review: Externally peer-reviewed.

DISCLOSURE

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REFERENCES

1. Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Res Ther. 2008; 10(5): 223.
2. Süzergöz F, Erdem AP, Sepet E, Bektaş M, Yalman N, Gürol AS. A pilot study on the isolation of dental pulp stem cells, potential of forming colonies and defining the content of stem cells. Türkiye Klinikleri J Med Sci. 2009; 29: 128-33.
3. Qi H, Aguiar DJ, Williams SM, La Pean A, Pan W, Verfaillie CM. Identification of genes responsible for osteoblast differentiation from human mesodermal progenitor cells. Proc Natl Acad Sci U S A. 2003; 100(6): 3305-10.
4. Minteer DM, Marra KG, Rubin JP. Adipose stem cells: biology, safety, regulation, and regenerative potential. Clin Plast Surg. 2015; 42(2):169-79.
5. Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. J Craniofac Surg. 2005; 16(6): 1043-54.
6. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003; 83(3): 835-70.
7. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg. 2004; 114(6): 1502-8.
8. Salkın H, Gönen ZB, Ergen E, Bahar D, Çetin M. Effects of TGF-β1 Overexpression on Biological Characteristics of Human Dental Pulp-derived Mesenchymal Stromal Cells. Int J Stem Cells. 2019; 12(1): 170-82.
9. Lucarelli E, Beccheroni A, Donati D, Sangiorgi L, Cenacchi A, Del Vento AM, et al. Platelet-derived growth factors enhance proliferation of human stromal stem cells. Biomaterials. 2003; 24(18): 3095-100.
10. Kocaoemer A, Kern S, Klüter H, Bieback K. Human AB serum and thrombin-activated platelet-rich plasma are suitable alternatives to fetal calf serum for the expansion of mesenchymal stem cells from adipose tissue. Stem Cells. 2007; 25(5): 1270-8.
11. Vogel JP, Szalay K, Geiger F, Kramer M, Richter W, Kasten P. Platelet-rich plasma improves expansion of human mesenchymal stem cells and retains differentiation capacity and in vivo bone formation in calcium phosphate ceramics. Platelets. 2006; 17(7): 462-9.
12. Doucet C, Ernou I, Zhang Y, Llense JR, Begot L, Holy X, et al. Platelet lysates promote mesenchymal stem cell expansion: a safety substitute for animal serum in cell-based therapy applications. J Cell Physiol. 2005; 205(2): 228-36.
13. Lee JY, Nam H, Park YJ, Lee SJ, Chung CP, Han SB, et al. The effects of platelet-rich plasma derived from human umbilical cord blood on the osteogenic differentiation of human dental stem cells. In Vitro Cell Dev Biol Anim. 2011; 47(2): 157-64.
14. Stessuk T, Puzzi MB, Chaim EA, Alves PC, de Paula EV, Forte A, et al. Platelet-rich plasma (PRP) and adipose-derived mesenchymal stem cells: stimulatory effects on proliferation and migration of fibroblasts and keratinocytes in vitro. Arch Dermatol Res. 2016; 308(7): 511-20.
15. Seyhan N, Alhan D, Ural AU, Gunal A, Avunduk MC, Savaci N. The effect of combined use of platelet-rich plasma and adipose-derived stem cells on fat graft survival. Ann Plast Surg. 2015; 74(5): 615-20.
16. Shen J, Gao Q, Zhang Y, He Y. Autologous platelet rich plasma promotes proliferation and chondrogenic differentiation of adipose derived stem cells. Mol Med Rep. 2015; 11(2): 1298-303.
17. Pak J, Chang JJ, Lee JH, Lee SH. Safety reporting on implantation of autologous adipose tissue-derived stem cells with platelet-rich plasma into human articular joints. BMC Musculoskelet Disord. 2013; 14: 337.
18. Van Pham P, Bui KH, Ngo DQ, Vu NB, Truong NH, Phan NL, et al. Activated platelet-rich plasma improves adipose-derived stem cell transplantation efficiency in injured articular cartilage. Stem Cell Res Ther. 2013; 4(4): 91.
19. Man Y, Wang P, Guo Y, Xiang L, Yang Y, Qu Y, et al. Angiogenic and osteogenic potential of platelet-rich plasma and adipose-derived stem cell laden alginate microspheres. Biomaterials. 2012; 33(34): 8802-11.
20. Xie X, Wang Y, Zhao C, Guo S, Liu S, Jia W, et al. Comparative evaluation of MSCs from bone marrow and adipose tissue seeded in PRP-derived scaffold for cartilage regeneration. Biomaterials. 2012; 33(29): 7008-18.
21. Sell SA, Wolfe PS, Ericksen JJ, Simpson DG, Bowlin GL. Incorporating platelet-rich plasma into electrospun scaffolds for tissue engineering applications. Tissue Eng Part A. 2011; 17(21-22): 2723-37.
22. Felthaus O, Prantl L, Skaff-Schwarze M, Klein S, Anker A, Ranieri M, et al. Effects of different concentrations of Platelet-rich Plasma and Platelet-Poor Plasma on vitality and differentiation of autologous Adipose tissue-derived stem cells. Clin Hemorheol Microcirc. 2017; 66(1): 47-55.

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Does Awake Open Shoulder Surgery Provide Advantages for Time and Cost-Efficiency? A Single Center Experience

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Abstract

BACKGROUND/AIMS: Operating room usage time and the preferred anesthesia technique for surgery are among the factors affecting total hospital costs. Regional or general anesthesia may be preferred during shoulder surgery. This study investigated comparisons in time and the cost-effectiveness between ultrasonography-guided regional anesthesia and general anesthesia for open shoulder surgery.

MATERIALS AND METHODS: Data of those patients who underwent open shoulder surgery between August, 2021 and March, 2022 were evaluated retrospectively. Ultrasonography-guided interscalene and superficial cervical plexus blocks were preferred for awake open shoulder surgery and the middle trunk block was added to this combination. Regional anesthesia was compared with general anesthesia in terms of time and cost-effectiveness.

RESULTS: The data of 22 patients in the regional anesthesia group (group RA) and 28 patients in the general anesthesia group (group GA) were included in this study. The descriptive data and surgery types were similar between the groups ($p>0.05$). The Operating Room Usage Costs, Equipment and Medication Costs and total costs were significantly lower in the group RA compared to the group GA ($p=0.00012$, $p=0.00025$, $p=0.00001$, respectively). There was a statistically significant difference between the two groups with regards to the time of anesthesia administration and positioning (3.77 ± 1.47 vs 12.82 ± 1.72 minutes, $p<0.0001$), and the total operating room usage time (65.68 ± 21.18 vs 98.78 ± 34.43 minutes, $p=0.0001$).

CONCLUSION: In our study, it was shown that the operating room usage time and cost in awake open shoulder surgeries were less than surgeries performed under general anesthesia.

Keywords: Cost-effectiveness, regional anesthesia, shoulder

INTRODUCTION

Shoulder pain is an important clinical condition in pain medicine. Depending on the severity of the pain and/or the type of pathology, surgery may be required.[1,2] Repair of the shoulder capsule by means of open or arthroscopic procedures is a common orthopedic procedure.[3] In recent years, minimally invasive arthroscopic procedures have become increasingly popular due to their positive features such as wound healing, postoperative recovery quality, and length of hospital stay. However, because of its lower cost and the limited effect of its surgical approach on healing quality, open repair is still a frequently selected method in many facilities.[4-6]

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Although there are a few publications in the literature which express contrasting viewpoints, it has been reported that open shoulder surgery is generally more cost-effective, and the majority of studies regarding cost-effectiveness have focused on the surgical approach.[4] Regional anesthesia is routinely utilized during awake shoulder surgery. For this, interscalene block, superficial cervical block, suprascapular block, or axillary block can be used alone or in combination.[7-9] Some studies have suggested that awake shoulder surgery with an interscalene block is more advantageous with regards to cost when compared to using general anesthesia.[10] However, the success rate, potential complications, and patient satisfaction with interscalene block applications in awake shoulder surgery remain a subject of debate.[11] Diaphragm sparing is recommended for regional anesthesia techniques applied in both awake surgery and perioperative analgesia in shoulder surgery.[12]

In this study, we aimed to examine the cost-effectiveness of the anesthetic strategy utilized during shoulder surgery, rather than focusing on the comparison of conventional or arthroscopic approaches in shoulder surgery. Also, we aimed for our data to be a feasibility study for a less conventional block combination used in awake shoulder surgery.

MATERIALS AND METHODS

Study Design

This study was designed as a retrospective data analysis. Approval from the Local Ethics Committee of Samsun Ondokuz Mayıs University Faculty of Medicine (approval number: 2022/152) was obtained and this study was registered at clinicaltrials.gov (NCT05406609) prior to its commencement. Our study is based on data from the FONET, Hospital Information Management System, v4.22.6.1, Türkiye database, in which patients who had shoulder surgery between August 1st, 2021 and March 31st, 2022 were evaluated. The patients received either general anesthesia or regional anesthesia according to the anesthesiologists experience and the availability of the technical devices at the time of their surgery. As the data was collected retrospectively from this data pool, no randomized sampling was possible. All of the patients who were operated on between the selected dates were planned to be included in this study. The data of those patients who underwent arthroscopic or emergency surgery, those <18 years of age, those who received peripheral nerve blocks for perioperative analgesia and those whose records were missing or incomplete were excluded from this study. The patients were grouped according to whether they underwent shoulder surgery under either regional anesthesia (group RA) or general anesthesia (group GA). After the inclusion and exclusion criteria were applied, it was found that 22 patients had received regional anesthesia and 28 patients had received general anesthesia during the selected time period. All of these were then allocated to either group RA or group GA.

Data Collection

Data was gathered from the perioperative anesthetic follow-up form, which was recorded as standard for each procedure. Aside from general patient information such as age, gender, and American Society of Anesthesiologists Classification (ASA), the type of anesthesia, the surgical procedure, and the medicines and materials utilized by the anesthesia team were all recorded. The operating room utilization was assessed in four stages:

Time of anesthesia administration: time of induction, intubation, and time to commencement of mechanical ventilation,

Positioning time: to get the patient into the proper surgical position,

Surgical time: from the commencement of surgery until its completion,

Recovery time: between the end of the surgery and the patient leaving the operating room; extubation and recovery.

The total time is the sum of these four sections.

For the *total cost* calculation, the purchase costs of the medications and materials recorded in the hospital system, excluding those utilized within the scope of the surgical procedure, were obtained and calculated independently for each patient. The price information of the equipment and drugs was taken from the price data of 2021. For the purpose of the standardization of operating room working costs, a fixed value (constant/minute) was determined on a per-minute basis, excluding the salaries of the healthcare workers. Operating room usage cost was calculated by multiplying this fixed value by the minutes for which the operating room was utilized for each patient (constant multiplied by minutes).

General Anesthesia Protocol

Each patient received standard monitoring, which included 3-channel electrocardiography (ECG), non-invasive blood pressure, and pulse oximetry. For induction, 2% lidocaine 1 mg/kg, 1-2 mcg/kg fentanyl, 2-3 mg/kg propofol, and 0.6 mg/kg rocuronium were used. 1 minimum alveolar concentration sevoflurane or desflurane was used for anesthesia maintenance. While paracetamol 1 gr was routinely used for postoperative analgesia, the choice of nonsteroidal anti-inflammatory, single-dose intravenous opioid, or intravenous patient-controlled analgesia was at the discretion of the anesthetist. In our country (Türkiye), atropine and neostigmine are frequently used to reverse neuromuscular blockade, while sugammadex is used only when absolutely essential (difficult intubation, prolonged neuromuscular block etc.).

Regional Anesthesia Protocol

For open shoulder surgery, ultrasound-guided brachial plexus blocks such as interscalene and superficial cervical blocks are favored. In our practice, the middle trunk block is added to the interscalene and superficial cervical plexus blocks to avoid discomfort due to the arm abduction position used during awake shoulder surgery. Peripheral block applications are carried out in the peripheral block procedure room preoperatively. After standard monitoring, 0.01-0.02 mg/kg midazolam and 0.15 mg/kg ketamine are administered intravenously, for sedoanalgesia. Following sterile prep, the patient's head is rotated 30 degrees away from shoulder which is to be operated on. Using ultrasound guidance, a block needle is used to administer a total of 20-25 mL of a mixture of 1% lidocaine and 0.25% bupivacaine of which 6-8 mL is administered to the interscalene region, 8-10 mL to the superficial cervical region, and 6-8 mL between the middle and inferior trunks. Conventional superficial cervical plexus block is applied more cephalically than the point where interscalen block is applied. As a modified cervical plexus block, we fix the ultrasound transducer where the interscalen block is applied, and without making a second skin puncture, we perform the superficial servical plexus block on this plane. Furthermore, after this combined procedure, the ultrasound

transducer is located more caudally to the supraclavicular fossa where superior, middle and inferior trunks are identified sonoanatomically. A needle is advanced towards the middle trunk and local anesthetic solution is injected as it surrounds the trunk in circular manner.

Twenty minutes after block performance, the patient is transported to the operating room. In the operating room, the surgical site is evaluated for sensory block and, if successful, the surgical procedure is started.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 16.0 statistical package program (SPSS Inc.; Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were expressed as mean ± standard deviation. A univariate analysis compared means between the groups using a two-sample, Independent t-test assuming equal variances for continuous variables. Ratios were compared using the chi-squared test. For data without normal distribution, the Mann-Whitney U test was performed. A p-value<0.05 was considered statistically significant.

RESULTS

The data of the 164 patients who underwent shoulder surgery were evaluated. The data of 98 patients who underwent arthroscopy, 4 patients who were <18 y of age, and 12 patients who received peripheral nerve block for perioperative analgesia were excluded from this study. The remaining 50 patients were divided into group RA (n=22) and group GA (n=28), respectively (Figure 1). There was no significant difference between the two groups with regards to their demographics, including their ages, genders, and their ASA (Table 1). The surgery procedures are shown in Table 1.

All patients in group RA received peripheral nerve block as described previously. All blocks were successful and no complications were observed. Two patients reported mild perioperative pain and discomfort and were administered 1 mg/kg/hr propofol infusion. No increases in infusion rates were required in these patients. General anesthesia was not required in any of the patients.

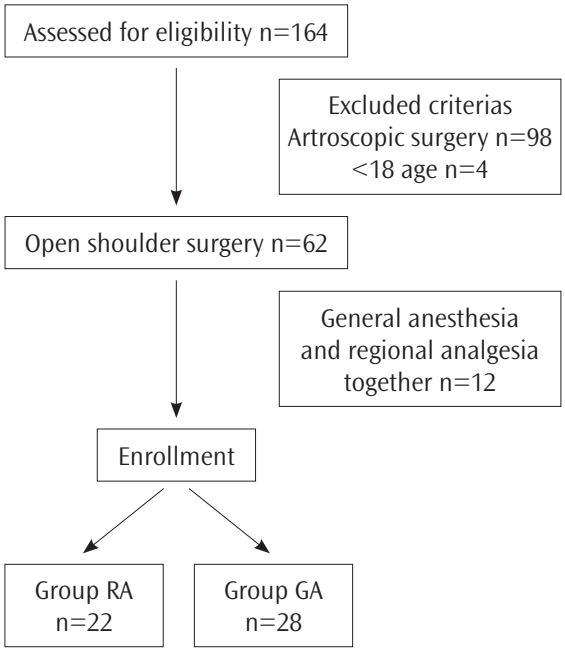

Figure 1. Flow chart of this study.

The surgical times were similar between group RA and group GA (61.9±21.84 vs 62.42±34.33 minutes, p=0.94). However, there was a statistically significant difference between the two groups with regards to time of anesthesia administration and positioning (group RA: 3.77±1.47 vs group GA: 12.82±1.72 minutes, p<0.0001), and the total operating room usage time (group RA: 65.68±21.18 vs group GA: 98.78±34.43 minutes, p=0.0001) (Table 2). The monitoring time of the patients on the operating table was accepted as being standard and not included in the analysis.

Comparisons of costs are shown in Table 2 and Figure 2. Equipment and medication costs (120.67±7.76 vs 205.95±106.89 TL, p=0.00025) as well as total operating room costs (1,090.31±351.59 vs 1,639.84±571.55 TL, p=0.00012) were found to be higher in group GA when compared to group RA. Similarly, total costs were higher in group GA (p=0.00001).

A detailed list of the materials and medicines used included in the cost-calculation per group is given in Table 3.

DISCUSSION

Our study demonstrated that regional anesthesia techniques, when used as the primary anesthetic method in patients undergoing open shoulder surgery, are more cost-effective and significantly reduce the amount of time spent in the operating room, when compared to the use of general anesthesia. Additionally, our study demonstrated that the regional anesthesia combination described in this study and utilized in our clinic is a viable anesthetic technique for open shoulder surgery.

Ultrasound-guided regional anesthesia techniques can be a beneficial option, especially in orthopedic surgeries. Anesthesia for awake shoulder surgery can be achieved with interscalene block applied with a relatively high volume of LA (20 mL and above), but since respiratory complications such as hemidiaphragmatic paralysis are common, clinicians have sought phrenic nerve sparing techniques.[7,13-16] There are many studies reporting that techniques such as the combination of suprascapular nerve and axillary nerve block, sub-omohyoidal plane block, etc. have similar effects to interscalene block in postoperative analgesia, but it is not possible to use these techniques as the main anesthetic method.[15,17]

The superficial cervical plexus and the brachial plexus actively participate in the innervation of the region affected by shoulder surgery.[18] With high volume interscalene block, spread to both plexuses occurs, and effective anesthesia can be achieved.[14,19] In our clinic, we apply a combination of 20-25 mL of LA with interscalene block (6-8 mL), modified superficial cervical plexus block (8-10 mL) and selective trunk block (6-8 mL between middle and inferior). To the best of our knowledge, there exists no data on the use of such a combination in shoulder surgery. This combination was chosen in order to achieve sensory blockade in all areas which may cause perioperative pain in open shoulder surgery, and to achieve complete sensory/motor blockage of the arm on the relevant side, reducing the patient's exposure to discomfort during perioperative shoulder-arm-hand manipulations and thus, to increase patient satisfaction.

Cost studies in shoulder surgeries have mostly focused on the cost of the surgical procedure.[4,5] However, when total hospital expenses

Table 1. Patient demographics and Surgery Types based on the groups

		Group RA, (n=22)	Group GA, (n=28)	p
Age (year)		58.5±7.5	60±12.5	0.6
Gender (F/M)		12/10	19/9	0.92
ASA*	I	1	3	0.51
	II	18	19	
	III	3	6	
Type of surgery	Rotator cuff repair	2	1	0.62
	Rotator cuff repair and acromioplasty	16	13	
	Others (fracture, neoplasm, etc.)	4	14	

*ASA: American Society of Anesthesiologists Classification.

Table 2. Comparisons of perioperative times and costs according to groups

	Group RA, (n=22)	Group GA, (n=28)	p
Anesthesia Administration time (m*)	0.0±0.0	8.53±2.2	N/A
Positioning time (m)	3.77±1.47	12.82±1.72	**<0.0001**
Surgical time (m)	61.9±21.84	62.42±34.33	0.94
Operating room usage time (m)	65.68±21.18	98.78±34.43	**0.00012**
Operating room usage cost (TL**)	1,090.31±351.59	1,639.84±571.55	**0.00012**
Equipment and medication costs (TL)	120.67±7.76	205.95±106.89	**0.00025**
Total costs (TL)	1,210.99±354.25	1,845.80±576.08	**0.00001**

*m: minutes, **TL: Turkish Lira.

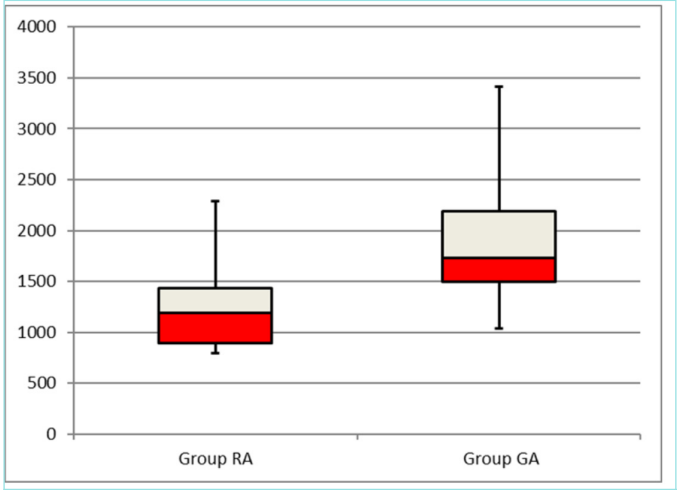

Figure 2. Box plot of total costs based on groups.

Distribution of total costs by groups. Minimum, first quartile, median, third quartile and maximum are shown. Y axis; demonstrates the total cost (Turkish Lira).

are considered, anesthetic management has a significant financial impact.[20] Hadzic et al.[21] found that interscalene block combined with low-dose propofol reduced surgical time, postoperative pain scores, the incidence of sore throat, nausea, and vomiting, and the time to discharge when compared to general anesthesia. They authors reported that same-day discharge would significantly reduce hospital costs.[21] In our study, we found that operating room usage times were reduced by up to 33% when regional anesthesia was used in comparison to general anesthesia. We did not include the time to discharge as one of our study's outcomes, since no standardized discharge criteria exist for open shoulder procedures in our institute.

Regional anesthesia is no longer merely a patient-focused technique in contemporary anesthetic practice. Today, the term "*Green-gional*" anesthesia has been coined, as the use of regional anesthesia techniques theoretically reduces the use of volatile agents, and indirectly, with the reduction in greenhouse gas emissions, and places the application of regional anesthesia well beyond the costs of the "*hospital*" or the "*operation*".[22,23]

Regional anesthesia techniques - whether for postoperative analgesia or as the primary anesthetic method - provide effective analgesia in the first postoperative hours, prevent muscle spasm, permit early mobilization of the shoulder joint, and enable early initiation of physiotherapeutic treatment.[24,25] In our study, however, we did not consider the potential long-term benefits or treatment expenses, especially those regarding postoperative physiotherapy. In addition, early mobilization was not performed on all patients, as this was a retrospective study which covered various types of open shoulder procedures. However, more comprehensive data can be gained through multidisciplinary research involving long-term evaluations and follow-ups after shoulder surgery. It should be noted that regional anesthetic procedures should not be presented as being fully harmless. Some studies have attributed complex regional pain syndrome following shoulder surgery to a complication of interscalene block.[26] It would be more appropriate to evaluate the postoperative effects of varying regional anesthesia techniques in homogenized patient groups and then to examine issues such as cost, postoperative chronic pain development, and early mobilization with comparative studies.

Study Limitations

Our study has some limitations. First of all, the study's retrospective design could have caused bias. In addition, even though all of the patients in this study underwent open shoulder surgery, their pathologies varied, leading to heterogeneity. Stronger findings can be

Table 3. Detailed List of materials and medicines included in cost-calculation per group

Medicine			Equipment	
Group RA	Group GA		Group RA	Group GA
Fentanyl 1-2 µg/kg	Fentanyl 1-2 µg/kg	Hypertonic fluid 500 mL/h	ECG pallet n=3	ECG pallet n=3
Midazolam 0.03 mg/kg	Midazolam 0.03 mg/kg	Ondansetron 4 mg	Injector 5 mL/20 mL	Injector 2 mL/5 mL/10 mL/20 mL
Lidocaine 2% 1-2 mg/kg (RA)	Lidocaine 2% 1 mg/kg (i.v.)	Proton pump inhibitor 40 mg	Intravenous cannula 20 G	Intravenous cannula 20 G
Paracetamol 1 g	Paracetamol 1 g	Atropine 0.01-0.03 mg/kg	Fluid line n=1	Fluid line n=1
Glyceryl trinitrate 1 µg/kg*	Glyceryl trinitrate 1 µg/kg*	Neostigmine 0.02-0.03 mg/kg	Oxygen mask n=1	Anesthetic face mask n=1
Dexamethasone 8 mg	Dexamethasone 8 mg	Theophylline 200 mg	Peripheral nerve block needle n=1	Airway n=1
Ephedrine 0.1 mg/kg**	Ephedrine 0.1 mg/kg**	Methylprednisolone 0.5-1 mg/kg		Endotracheal tube n=1
Metoprolol tartrate 5 mg***	Metoprolol tartrate 5 mg***	Sevoflurane 13 mL/h		Bacteria filter n=1
Saline 1,000 mL/h	Saline 1,000 mL/h	Desflurane 34.2 mL/h		Aspiration probe n=1
Propofol 0.5-1 mg/kg	Propofol 1.5-2.5 mg/kg	Sugammadex 2 mg/kg[4]		Ventilation line n=1
Ketamine 1-2 mg/kg	Rocuronium bromide 0.6 mg/kg	Tetracycline pomade Eye protection		
Bupivacaine 0.5% 0.5-1 mg/kg (RA)	Remifentanil 0.05-0.2 µg/kg/min	Tramadol 100 mg		
		NSAID 50 mg		

*If arterial blood pressure increases 20-30% more than preoperatively. **If arterial blood pressure decreases 20-30% more than preoperatively. ***If heart rate increases 20-30% more than preoperatively. [4]If there are some contraindications for the use of atropine and neostigmine. All of the materials are not used in all patients. They are used as needed selectively. ECG: Electrocardiography

achieved from a cost-effectiveness analysis which uses the same surgical technique, possibly even performed by the same surgeon, to treat the same clinical condition. However, the viability of our findings in terms of cost effectiveness, time effectiveness, and regional anesthesia combinations in awake shoulder surgery seems plausible. Our inability to reveal the postoperative analgesic requirements and long-term follow-up results and also not being able to include the wages of the personnel who worked in the operating and block rooms are the other limitations. Furthermore, although there were no unsuccessful blocks in our study, there is always a probability of an unsuccessful block because of anatomical variations or the lack of experience of the block operator. This may cause an increase in costs. This situation may be evaluated as another limitation.

CONCLUSION

In our study, it was shown that the operating room usage times and costs in awake open shoulder surgeries were less than surgeries performed under general anesthesia. However, further prospective, randomized and controlled studies are needed.

MAIN POINTS

- Ultrasound guided regional anesthesia techniques can be a useful option in orthopedic surgeries.
- The use of regional anesthesia techniques during shoulder surgery can be more cost-effective than general anesthesia and can significantly reduce the time spent in the operating room.
- The combination of interscalene block, modified superficial cervical plexus block and selective trunk block applied in our clinic can be used as a suitable anesthesia technique for open shoulder surgery.

Ethics Committee Approval: This study was approved by the Local Ethics Committee of Samsun Ondokuz Mayıs University Faculty of Medicine (approval number:2022/152).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S., Concept: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S., Design: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S., Data Collection and/or Processing: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S., Analysis and/or Interpretation: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S., Literature Search: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S., Writing: D.A., S.T., M.Ü., A.E., N.G., Ş.C.A., H.B.A., M.S.

DISCLOSURES

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

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REFERENCES

1. Chan CW, Peng PW. Suprascapular nerve block: a narrative review. Reg Anesth Pain Med. 2011; 36(4): 358-73.
2. Chaudhury S, Gwilym SE, Moser J, Carr AJ. Surgical options for patients with shoulder pain. Nat Rev Rheumatol. 2010; 6(4): 217-26.
3. Milano G, Grasso A. Shoulder Arthroscopy: Principles and Practice. Springer Science & Business Media; 2013. p.622.
4. Adla DN, Rowsell M, Pandey R. Cost-effectiveness of open versus arthroscopic rotator cuff repair. J Shoulder Elbow Surg. 2010; 19(2): 258-61.

5. Akcal MA, Ozturk N, Isıkcelık F, Agırbas I. Cost-effectiveness analysis of arthroscopic surgery versus open surgery in rotator cuff repair. Marmara Med J. 2021; 34(1): 66-71

6. Murphy J, Gray A, Cooper C, Cooper D, Ramsay C, Carr A. Costs, quality of life and cost-effectiveness of arthroscopic and open repair for rotator cuff tears: an economic evaluation alongside the UKUFF trial. Bone Joint J. 2016; 98-B(12): 1648-55.

7. Hewson DW, Oldman M, Bedforth NM. Regional anaesthesia for shoulder surgery. BJA Educ. 2019; 19(4): 98-104.

8. Vijayakumar V, Ganesamoorthi A, Subramaniyan N, Kasirajan P. Ultrasound-Guided Superior and Middle Trunk Brachial Plexus Block with Superficial Cervical Plexus Block for Shoulder Surgeries in High-Risk Patients: Case Series. J Med Ultrasound. 2020; 28(3): 185-7.

9. Sivakumar RK, Areeruk P, Karmakar MK. Selective trunk block (SeTB): a simple alternative to hybrid brachial plexus block techniques for proximal humeral fracture surgery during the COVID-19 pandemic. Reg Anesth Pain Med. 2021; 46(4): 376-8.

10. Gonano C, Kettner SC, Ernstbrunner M, Schebesta K, Chiari A, Marhofer P. Comparison of economical aspects of interscalene brachial plexus blockade and general anaesthesia for arthroscopic shoulder surgery. Br J Anaesth. 2009; 103(3): 428-33.

11. Tian T, Li XT, Xue FS. Comparing postoperative benefits and risks of single and continuous interscalene block for signle and continuous interscalene block for shoulder surgery. J Shoulder Elbow Surg. 2022; 31(9): E460-1

12. Nair A, Diwan S. Erector spinae block as a phrenic nerve sparing block for shoulder surgeries. Regional Anesthesia & Pain Medicine. 2020; 45: 751-2

13. Bishop JY, Sprague M, Gelber J, Krol M, Rosenblatt MA, Gladstone J, et al. Interscalene regional anesthesia for shoulder surgery. J Bone Joint Surg Am. 2005; 87(5): 974-9.

14. Bishop JY, Sprague M, Gelber J, Krol M, Rosenblatt MA, Gladstone JN, et al. Interscalene regional anesthesia for arthroscopic shoulder surgery: a safe and effective technique. J Shoulder Elbow Surg. 2006; 15(5): 567-70.

15. Pitombo PF, Meira Barros R, Matos MA, Pinheiro Módolo NS. Selective suprascapular and axillary nerve block provides adequate analgesia and minimal motor block. Comparison with interscalene block. Braz J Anesthesiol. 2013; 63(1): 45-51.

16. Tran DQ, Layera S, Bravo D, Cristi Sanchez I, Bermudez L, Aliste H. Diaphragm-sparing nerve blocks for shoulder surgery, revisited. Regional Anesthesia & Pain Medicine. 2020; 45: 73-8.

17. Abdallah FW, Wijeysundera DN, Laupacis A, Brull R, Mocon A, Hussain N, et al. Subomohyoid Anterior Suprascapular Block versus Interscalene Block for Arthroscopic Shoulder Surgery: A Multicenter Randomized Trial. Anesthesiology. 2020; 132(4): 839-53.

18. Rapp FA, Soos MP. Anatomy, Shoulder and Upper Limb, Hand Cutaneous Innervation. StatPearls [Internet]. 2022.

19. Panchagnula, U, Sagadai S, Columb M. Complications of interscalene brachial plexus block following shoulder surgery in the awake sitting position: 8AP2-3. European Journal of Anaesthesiology. 2007; 24: 89.

20. Childers CP, Maggard-Gibbons M. Understanding Costs of Care in the Operating Room. JAMA Surg. 2018; 153(4): e176233

21. Hadzic A, Williams BA, Karaca PE, Hobeika P, Unis G, Dermksian J, et al. For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. Anesthesiology. 2005; 102(5): 1001-7.

22. Özelsel TJP, Ip VHY, Sondekoppam RV. "Green-gional" anesthesia: a lot greener than you think. Regional Anesthesia & Pain Medicine. 2021; 46: 553-4.

23. Kuvadia M, Cummis CE, Liguori G, Wu CL. 'Green-gional' anesthesia: the non-polluting benefits of regional anesthesia to decrease greenhouse gases and attenuate climate change. Reg Anesth Pain Med. 2020; 45(9): 744-5.

24. Beecroft CL, Coventry DM. Anaesthesia for shoulder surgery. Contin Educ Anaesth Crit Care Pain. 2008; 8(6): 193–8.

25. Mazuquin B, Moffatt M, Gill P, Selfe J, Rees J, Drew S, et al. Effectiveness of early versus delayed rehabilitation following rotator cuff repair: Systematic review and meta-analyses. PLoS One. 2021; 16(5): e0252137

26. Magone KM, Ben-Ari E, Hacquebord JH, Virk MS. Complex Region Pain Syndrome Following Shoulder Surgery. Arthrosc Sports Med Rehabil. 2021; 3(4): e1037-45.

RESEARCH ARTICLE

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Analysis of Endometrial Cancer in Premenopausal Women: Single-Centre Experience

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Abstract

BACKGROUND/AIMS: To evaluate the clinocopathological characteristics, treatment, and survival of premenopausal women with endometrial cancer (EC).

MATERIALS AND METHODS: The study sample retrospectively included 107 women under 50 years of age who had undergone surgical treatment for EC at a single centre.

RESULTS: We identified 107 premenopausal women with EC. Their median age was 46 (range: 34-49) years, and their mean body mass index was 33 (range: 19-65) kg/m^2. Fifty-nine women (55.1%) were nulliparous and 22 women (20.5%) reported a history of polycystic ovary syndrome. There were ninety-one (85%) young women (premenopausal) having <50% myometrial invasion (MI), sixteen women (15%) having ≥50 MI and ninety women (84.2%) with grade 1 or 2 endometrioid histology, and seventeen women (15.8%) with grade 3 endometrioid histology. Ninety-five (88.8%) women had stage 1-2 disease (1-2 early disease) and 12 (11.2%) women had stage 3-4 (advanced-stage) disease.

CONCLUSION: <50% MI, grade 1-2 and early stage (stage 1-2) endometrioid type EC were more common in young premenopausal patients. Additionally, most of the patients were obese and nulliparous in this age group.

Keywords: Endometrial cancer, premenopausal women, CA125, LVSI, adjuvant treatment

INTRODUCTION

Endometrial cancer (EC) is the most common cancer of the female reproductive system worldwide.[1] EC is mostly diagnosed in the postmenopausal period, and the median age at diagnosis is 62 years. However, up to 14% of patients with EC are diagnosed during the premenopausal period.[2] Women of advanced age with EC are often diagnosed via endometrial sampling early in the course of their disease with the common complaint of postmenopausal bleeding. However, irregular bleeding is common in the premenopausal age group and the diagnosis of EC may be delayed.[3] Chronic ovulation results in a thickening of the endometrial tissue due to unopposed estrogen and this is a risk factor for EC. Other risk factors for EC in premenopausal women include obesity, hypertension, nulliparity, impaired glucose intolerance, polycystic ovary syndrome (PCOS), menstrual irregularities, and a history of infertility.[4] Obesity increases the release of estrogen from adipose tissue in premenopausal women, significantly increasing the risk of EC. The risk of AK cancer increases three-fold in women who exceed normal body weight by 9-23 kg and ten-fold in women with an excess of 23 kg over the normal body weight.[5]

Young age, histologic endometrioid type grade 1 or 2, and low stage are good prognostic factors for EC.[6] Premenopausal EC is associated with 5-year survival rates of over 95% and good prognoses in premenopausal patients.[7] The standard treatment for EC is hysterectomy, bilateral salpingo-oophorectomy, possible lymphadenectomy, and omentectomy. Endometrioid endometrial carcinoma (EEC) accounts for 70% to 80% of

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all ECs.[8] Few published studies have investigated those patients with premenopausal EEC, and most such studies have had small sample sizes. We aimed to assess the clinical, pathologic, and prognostic factors associated with EEC in premenopausal patients aged <50 years.

MATERIALS AND METHODS

The records of those patients who had undergone treatment for EC in the gynecologic oncology clinic of the University of Health Sciences City Hospital between January, 2007 and January, 2018 were evaluated retrospectively. Ethics committee approval was obtained from Ankara Zekai Tahir Burak Training and Research Hospital Non-Interventional Clinical Research Ethics Committee under the Declaration of Helsinki (approval number: 2018/20). Written informed consent for the use of medical information for investigative intent was obtained. Clinical information was obtained from our institution's electronic medical records. This study's sample included a total of 107 women under 50 years of age with EC who had undergone surgical treatment for endometrioid-type EC (EEC) according to their final pathology reports. We excluded those patients older than 50 years with endometrioid-type EC, those with non-endometrioid-type EC, and those with the presence of synchronous malignancies according to their final pathology reports. Women under 50 years of age with a follicle-stimulating hormone (FSH) levels <30 IU/L and/or an irregular menstrual cycle were considered premenopausal and included in this study. Women who had not had menstrual bleeding within 6 months to 1 year and whose serum FSH levels were >30 IU/L were considered menopausal and were excluded from this study.[9] Additionally, those receiving neoadjuvant chemotherapy or primary radiation therapy and those with incomplete medical records were excluded. The following data were collected retrospectively from the files and electronic data of the patients in this study: age, date of operation, International Federation of Gynaecology and Obstetrics (FIGO) stage, menopausal status, preoperative cancer antigen (CA125) levels, lymphovascular space invasion (LVSI) status, type of surgical treatment, lymphadenectomy status, presence of recurrence (loco-regional, retroperitoneal, distant), adjuvant treatment received (radiotherapy, chemotherapy, and chemo-radiotherapy), brachytherapy history, time to recurrence, survival status, and follow-up period until January, 2018. Prior to 2014, all patients diagnosed with EC underwent staging surgery, which included hysterectomy, bilateral salpingo-oophorectomy, and systematic retroperitoneal (pelvic and para-aortic) lymphadenectomy. Starting in 2014, retroperitoneal lymphadenectomy was performed according to the results of intraoperative frozen section analysis for those women who met the Mayo Clinic Criteria.[10] LVSI is defined as the presence of tumour cells within the lymphatics or capillaries.[11] We followed up the patients every 3 months for the first 2 years, twice a year for the next 3 years, and once a year for the next 5 years. Pelvic examinations were performed at each outpatient visit. Disease-free survival (DFS) was defined as the time interval between surgery and the first recurrence of EC. Overall survival (OS) was defined as the time from surgery to death or the last outpatient visit.

Statistical Analysis

Cox regression analysis was used to identify independent prognostic factors for DFS and OS. The Kaplan-Meier method was used for survival analysis. A p-value <0.05 was accepted as being statistically significant. Statistical calculations were performed using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

We identified 107 women according to the inclusion criteria. Their median age was 46 (range: 34-49) years. Their median follow-up duration was 58.0 (range: 12-144) months. The patient demographic and clinicopathological characteristics are summarized in Table 1. Their mean body mass index (BMI) was 33 (range: 19-65) kg/m^2; 57% of the patients had a BMI ≥30 kg/m^2. Fifty-nine women (55.1%) were nulliparous. Thirty (35.5%) had a history of irregular menstrual cycles. Twenty-two women (20.5%) reported a history of PCOS. Twenty-three women (21.4%) had diabetes, and twenty-one women (19.6%) had hypertension. Their FIGO stages are presented in Table 1. Histologic grades 1, 2, and 3 of the disease were reported in 74 (69.2%), 16 (15%), and 17 (15.8%) patients, respectively. Ninety-one women (85%) had <50 myometrial invasion (MI), and sixteen women (15%) had ≥50 MI. Ninety-five (88.8%) women had stage 1-2 disease (1-2 early disease) and 12 (11.2%) women had stage 3-4 (advanced-stage) disease. There were 29 patients (27.1%) with EC who had undergone total hysterectomy ± bilateral salpingo-oophorectomy only. Lymphadenectomy was performed in 78 patients (72.9%). Eighty-seven patients (81.3%) did not receive adjuvant treatment. Twenty patients (14.9%) received postoperative adjuvant therapy, eight patients (7.2%) received chemo-radiotherapy, and four patients (3.6%) received only chemotherapy. In the entire cohort, the 5-year DFS and OS rates were 96.4% and 98.2%, respectively. Results of the univariate analysis results for the demographic and clinic-pathological characteristics associated with DFS are presented in Table 2. Univariate analysis revealed that DFS was significantly lower among those patients with stage 3-4 disease ($p<0.001$), grade 2-3 histology ($p<0.001$), and those with the presence of LVSI ($p=0.002$) and lymph node metastasis ($p<0.001$) (Table 2). Univariate analysis revealed that OS was significantly lower among those patients with stage 3-4 disease ($p=0.004$), grade 2-3 histology ($p=0.007$), and those with the presence of LVSI ($p=0.018$) and lymph node metastasis ($p<0.001$). The multivariate analysis revealed no independent predictors for prolonged DFS or OS.

DISCUSSION

EC is usually diagnosed in postmenopausal women, but there is a significant proportion of ECs diagnosed in premenopausal women younger than 50 years of age. Premenopausal EC may be difficult to diagnose because irregular vaginal bleeding can frequently be as a result of menstrual irregularities and hormonal disorders.[11] Age is in important prognostic factor in EC patients. Young patients with EC have more favourable prognoses than older patients. For this reason, it is important to diagnose and treat the premenopausal EC age group. In this study, we evaluated patients under 50 years of age with EC at a single centre over a period of 12 years. The major findings of our study included that premenopausal EC is associated with better clinicopathological prognostic characteristics, including earlier stages, lower tumour grades, less MI, and the absence of LVSI and lymph node involvement. Recent studies have shown that patient age, advanced FIGO stage, high grade, deep MI, the presence of cervical stromal invasion, and the presence of LVSI increase the risk of extrauterine disease and nodal metastases and that these factors are associated with poor prognosis.[12-14] Benedetti Panici et al.[15] demonstrated that older age was a significant poor prognostic factor for OS and cancer-specific survival. The authors showed that being aged ≥65 years among EC patients was a poor prognostic factor, associated with their tumour grade and tumour stage, in terms of OS (5-year OS 92.1% for patients <65 years old vs. 78.4% for patients ≥65 years old). Premenopausal patients had better

Table 1. The demographic and clinicopathological characteristics of all patients (n=107)

Characteristics	Values, n (%)
Age (years), median	46 (34-50)
BMI	33 (19-65)
Baseline serum Ca125 (IU/mL)	28 (2-1,100)
Surgical treatment	
TAH + BSO	29/107 (27.1%)
TAH + BSO + staging	78/107 (72.9%)
Grade	
1	74/107 (69.2%)
2	16/107 (15 %)
3	17/107 (15.8 %)
Depth myometrial invasion, (n %)	
<%50	91/107 (85%)
≥%50	16/107 (15%)
Primary tumour diameter (cm), median	3 (0.1-8)
Peritoneal cytology, (n %)	
Positive	5/107 (4.7%)
Negative	102/107 (95.3%)
Cervical stromal invasion	
Yes	10/107 (93%)
No	97/107 (99.6%)
Adnexal involvement	
Yes	8/107 (7.5%)
No	99/107 (92.5%)
Number of LNs removed	45 (0-96)
Pelvic	31 (0-61)
Paraaortic	14 (0-40)
Stage	
1A	83/107 (77.6%)
1B	5/107 (4.7%)
2	7/107 (6.5%)
3A	3/107 (2.8%)
3B	-
3C	4/107 (3.7%)
4	5/107 (4.7%)
No additional treatment	87107 (81.3%)
Adjuvant treatment	
Brachytherapy only	6/107 (6.1%)
EBRT	1/107 (0.9%)
EBRT + brachytherapy	1/107 (0.9%)
Chemo-radiation	8/107 (7.2%)
Chemotherapy only	4/107 (3.6%)
Recurrence rates	5/107 (4.6%)
Status	
Alive	104/107
Died	3/107
Median follow-up time (months)	32 (3-68)

LN: Lymph node, LVSI: Lympho vascular space invasion, EBRT: External beam radiotherapy, TAH: Total abdominal hysterectomy + bilateral salpingo ooferectomy

prognoses in the presence of early stage and less MI. EC tends to have prognostically favourable histologic types, such as well-differentiated endometrioid type endometrial adenocarcinoma.[16,17] Lau et al.[18] found that perimenopausal EC patients had low-risk features, such as low-grade tumours, lymph node status, less MI, and endometrioid histology. Previous studies have revealed good prognostic features for ECs in the perimenopausal age group such as early stage, low grade, endometrioid histology, and less depth of MI.[4,19] We found that low-risk features, such as early-stage disease, less MI, and lower grade were more common in premenopausal patients with EC.

The PORTEC-1 study showed that patient age, histological grade, and deep MI were poor prognostic factors in terms of the recurrence and outlook for early-stage EC. They found a three-fold higher rate of recurrence among those patients aged ≥60 years.[12] Similarly, the Gynaecological Oncology Group-99 study found that age-related prognosis was worse in the older age group.[10] In our study, similar to postmenopausal status, the presence of lymph node metastasis, advanced stage, tumour size >2 cm, LVSI, and grade 2-3 differentiation were significantly associated with both shorter DFS and OS among premenopausal patients with EC.

Type 1 tumours are more common and are specifically more common during the premenopausal period. They are associated with clinical conditions which cause increased estrogen levels, as well as endometrioid-type EC with a better prognosis.[19] Type 2 ECs, on the other hand, are generally more aggressive, of the serous papillary or clear cell EC types, and are relatively rare in the postmenopausal period.[20]

According to the literature, the rate of early-stage (stage 1-2) EC is about 84.2-91% during the premenopausal period.[15,16] In our study, the rate of early-stage disease (stage 1-2) was 88.8%, which is similar to the findings of previous reports. Biler et al.[21] reported that high grade EC in younger patients had worse prognosis. Our study found that high-grade EC was associated with shorter DFS and OS.

Ayhan et al.[22] revealed that LVSI is an independent predictor of both OS and DFS among low-risk EC patients. The 5-year OS rate for those patients who had EC without LVSI was significantly higher than that of those patients who were LVSI-positive EC (98.5% vs. 88.2%, respectively).[22] In our study, only 15% of premenopausal patients with EC had LVSI. The overall 5-year DFS and 5-year OS rates were 97.3% and 98.8% among the LVSI-negative patients, respectively.

Obesity is strongly associated with the development of EC in the premenopausal age.[5] Recent studies have reported that estrogen, insulin levels, adipokines, growth factors, and many interrelated inflammatory factors may explain the link between obesity and increased EC risk.[23] A recent meta-analysis found a strong association between obesity and EC. Furthermore, a 5 kg/m^2 increase in BMI was significantly associated with higher EC risk. Notably, the obesity rate (57%) was high in our study.[24]

Previous studies reported that EC is more frequently associated with nulliparity, diabetes and hypertension in the premenopausal age group.[25,26] We saw similar outcomes among those women in the premenopausal age with EC; 55.1% were nulliparous, 21.4% had diabetes, and 19.6% had hypertension. This may be due to the high prevalence of obesity in those patients with EC in the premenopausal age group.

Table 2. Univariate analyses for disease free survival and overall survival in women <50 years with endometroid type endometrial carcinoma

	5 years (DFS)	Univariate, (p)	5 years (OS)	Univariate, (p)
Grade				
1	100%	<0.001	100%	**0.007**
2-3	82%		89.4%	
Stage				
1-2	97.8%	<0.001	98.8%	**0.004**
3-4	62.5%		82.5%	
Myometrial invasion				
<50%	98.8%	<0.001	98.8%	**0.016**
>50%	67.7%		86.5%	
Tumour size				
<3 cm	98.2%	0.107	100%	0.056
>3 cm	90.3%		93%	
Peritoneal cytology				
Positive	-	0.056	80%	**0.017**
Negative	95.5%		97.7%	
LVSI				
Yes	81.3%	0.002	87.1%	**0.018**
No	97.2%		98.8%	
CS involvement				
Yes	65.5%	<0.001	81.8%	**0.002**
No	97.8%		98.8%	
CA-125 (IU/mL)				
<35	97.8%	<0.001	98.9%	**0.001**
≥35	65.5%		80%	
LN involvement				
Yes	-	<0.001	60%	**<0.001**
No	97.3%		98.6%	
Adnexal involvement				
Yes	87.3%	0.253	87.5%	0.097
No	95.3%		97.7%	

DFS: Disease free survival, OS: Overall survival, LN: Lymph-node, LVSI: Lympho vascular space invasion, CC: Cervical stromal

Study Limitations

The main limitations of our study were its retrospective, single-centre design and its small sample size. Additionally, histopathological re-evaluation could not be performed. Despite these limitations, our study involved long-term follow-ups, and we believe that it is an important contribution to the literature in this field.

CONCLUSION

EC is uncommon in premenopausal patients, and it is usually early-stage, and it involves well-differentiated tumours. This age group has more favourable prognosis than elderly patients. In our study, obesity, diabetes, and hypertension rates were high, and EC risk could be reduced by changing dietary habits and lifestyles.

MAIN POINTS

- Obesity is associated with the development with EC in the premenopausal age.
- EC is uncommon in premenopausal patients and young patients.
- The absence of LVSI is a good prognostic indicator in premenopausal EC patients.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from Zekai Tahir Burak Training and Research Hospital Non-interventional Clinical Research Ethics Committee under the Declaration of Helsinki (approval number: 2018/20).

Informed Consent: Written informed consent for the use of medical information for investigative intent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: S.A., F.Y., Design: S.A., F.Y., Data Collection and/or Processing: S.A., Analysis and/or Interpretation: S.A., F.Y., Literature Search: S.A., Writing: S.A.

DISCLOSURES

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

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394-424.
2. Garg K, Soslow RA. Endometrial carcinoma in women aged 40 years and younger. Arch Pathol Lab Med. 2014; 138(3): 335-342.
3. Son J, Carr C, Yao M, Radeva M, Priyadarshini A, Marquard J, et al. Endometrial cancer in young women: prognostic factors and treatment outcomes in women aged ≤40 years. Int J Gynecol Cancer. 2020; 30(5): 631-639.
4. Soliman PT, Oh JC, Schmeler KM, Sun CC, Slomovitz BM, Gershenson DM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol. 2005; 105(3): 575-580.
5. Caponio MA, Addati T, Popescu O, Petroni S, Rubini V, Centrone M, et al. P16(INK4a) protein expression in endocervical, endometrial and metastatic adenocarcinomas of extra-uterine origin: diagnostic and clinical considerations. Cancer Biomark. 2014; 14(2-3): 169-175.
6. Bogani G, Dowdy SC, Cliby WA, Ghezzi F, Rossetti D, Frigerio L. Management of endometrial cancer: issues and controversies. Eur J Gynaecol Oncol. 2016; 37(1): 6-12.
7. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127(12): 2893-2917.
8. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol. 2000; 182(6): 1506-1519.
9. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al; STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012; 97(4): 1159-1168.
10. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al.; Gynecologic Oncology Group. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004; 92(3): 744-751.
11. Kansal Y, Bahadur A, Chaturvedi J, Rao S, Arora H, Kumari O, et al. Spectrum of abnormal uterine bleeding: Clinical patternand endometrial pathology aspects. J Gynecol Surg. 2018; 34: 12-17.
12. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000; 355(9213):1404-1411.
13. Kumar S, Mariani A, Bakkum-Gamez JN, Weaver AL, McGree ME, Keeney GL, et al. Risk factors that mitigate the role of paraaortic lymphadenectomy in uterine endometrioid cancer. Gynecol Oncol. 2013; 130(3): 441-445.
14. Guntupalli SR, Zighelboim I, Kizer NT, Zhang Q, Powell MA, Thaker PH, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol. 2012; 124(1): 31-35.
15. Benedetti Panici P, Basile S, Salerno MG, Di Donato V, Marchetti C, Perniola G, et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol. 2014; 210(4): 363.E1-363.E10.
16. Pellerin GP, Finan MA. Endometrial cancer in women 45 years of age or younger: a clinicopathological analysis. Am J Obstet Gynecol. 2005; 193(5): 1640-1644.
17. Chiva L, Lapuente F, González-Cortijo L, Carballo N, García JF, Rojo A, et al. Sparing fertility in young patients with endometrial cancer. Gynecol Oncol. 2008; 111: S101-104.
18. Lau HY, Chen YJ, Yen MS, Chao KC, Chen RF, Yeh SO, et al. Clinicopathological features and survival in young Taiwanese women with endometrial carcinoma. Int J Gynecol Cancer. 2014; 24(6): 1015-1020.
19. Koul A, Willén R, Bendahl PO, Nilbert M, Borg A. Distinct sets of gene alterations in endometrial carcinoma implicate alternate modes of tumori genesis. Cancer. 2002; 94(9): 2369-2379.
20. Voss MA, Ganesan R, Ludeman L, McCarthy K, Gornall R, Schaller G, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer-a clinical and pathological evaluation. Gynecol Oncol. 2012; 124(1): 15-20.
21. Solmaz U, Ekin A, Mat E, Gezer C, Dogan A, Biler A, et al. Analysis of clinical and pathological characteristics, treatment methods, survival, and prognosis of uterine papillary serous carcinoma. Tumori. 2016; 102(6): 593-599.
22. Ayhan A, Şahin H, Sari ME, Yalçin I, Haberal A, Meydanli MM. Prognostic significance of lymphovascular space invasion in low-risk endometrial cancer. Int J Gynecol Cancer. 2019; 29(3): 505-512.
23. Calle EE, Kaaks R. Over weight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004; 8: 579-591.
24. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mas index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet. 2008; 371(9612): 569-578.
25. Semaan A, Ali-Fehmi R, Munkarah AR, Bandyopadhyay S, Morris RT, Rizk S, et al. Clinical/pathologic features and patient outcome in early onset endometrial carcinoma: a population based analysis and an institutional perspective from the Detroit metropolitan area, Michigan. Gynecol Oncol. 2012; 124(2): 265-269.
26. Uharcek P, Mlyncek M, Ravinger J, Matejka M. Prognostic factors in women 45 years of age or younger with endometrial cancer. Int J Gynecol Cancer. 2008; 18(2): 324-328.

RESEARCH ARTICLE

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Gastrointestinal Follicular Lymphoma; Single Center 17 Years of Experience Results

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Eleven of the cases were presented orally at the 25th National Pathology Congress in 2015.

Abstract

BACKGROUND/AIMS: Primary gastrointestinal follicular lymphomas (PGIFL) are very rare among gastrointestinal non-Hodgkin lymphomas. In this study, we retrospectively examined the clinicopathological features of PGIFL and nodal follicular lymphoma with secondary gastrointestinal involvement (SGIFL) and to draw attention to these rare cases.

MATERIALS AND METHODS: Slides and blocks from cases of gastrointestinal follicular lymphoma (GIFL) between the years of 2006-2022 were obtained from the pathology archive. Pathology reports, demographic and clinical data, and endoscopic, and other imaging findings were accessed retrospectively from electronic records.

RESULTS: Eighteen of 31 GIFL cases were PGIFL, and 12 of them were SGIFL. In a case, detailed data could not be obtained. The female/male ratio was equal to PGIFL and SGIFL. The median age of PGIFL was 60, which is slightly higher than that of SGIFL. The most common endoscopic finding was polyp (61.1%) in PGIFL, and mass (50%) in SGIFL. Duodenum localization was 44.4% in PGIFL and 33.3% in SGIFL. Multiple lesions were detected 27.7% in PGIFL and 16.7% in SGIFL. 77.7% of PGIFL cases were stage I and low grade. Only one of the low-grade PGIFL cases was stage IV. Follicular dendritic cells (FDC) were pushed to the periphery in 72.2% of PGIFL, whereas this rate was 8.3% in SGIFL. CD20, CD10, bcl6, and bcl2 were positive and CD5, CD3, cyclin D1 were negative in all cases.

CONCLUSION: PGIFL cases are often localized in the duodenum, usually low grade, and extremely rare. Microscopically, the only difference between PGIFL and SGIFL is the pattern of the FDC.

Keywords: Lymphoma, follicular, gastrointestinal tract

INTRODUCTION

About one-third of non-Hodgkin lymphomas (NHL) develop from tissues other than the lymph nodes. These cases are called extranodal lymphoma (ENL). ENL is still a confusing issue, especially in cases where both nodal and extranodal diseases coexist. Primary nodal disseminated disease may have secondary extranodal spread, as well as primary ENL may tend to spread.[1,2] Thus, the rates in studies are more variable compared with nodal lymphomas. In the literature, it was shown that the ENL rate can vary between 20% and 34% depending on the selection of different criteria.[3]

The gastrointestinal (GI) tract is the most common site for ENLs. Different criteria have been proposed in the past by various authors to categorize primary gastrointestinal lymphoma (PGIL). Recently, it

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is widely accepted that cases with a clinically dominant extranodal component, no peripheral nodal component or minor involvement are considered as extranodal.[2] The Lugano system is widely used in staging (Table 1).[4]

Primary gastrointestinal follicular lymphoma (PGIFL) cases are extremely rare and are usually detected incidentally. It has been increasing recently because of the widespread usage of capsule and double-balloon endoscopy methods that make multiple biopsies possible.[5,6] PGIFL accounts for 1-13% of PGIL.[1,6-9]

PGIFL was accepted as a variant of follicular lymphoma (FL) in the 2008 version of the World Health Organization (WHO).[10] In the 2017 WHO classification, it was named duodenal -type follicular lymphoma (D-FL) and defined as a new entity with different clinical and pathological features compared with systemic FL.[11] In the 2022 update, the 5th version of WHO and ICC, it remains an entity of classical FL.[12,13] In the following sections of this article, PGIFL will be referred to as D-FL in accordance with the new terminology.

D-FL is more common in middle -aged adults. The median age is 56, and the age ranging is between 26-81.[1] While some case series of D-FL showed mild female predominance,[7,14,15] an equal gender distribution was observed in other case series.[6,16-20]

Although D-FL can develop from any area of the GI, its localization is the duodenum (especially the 2nd part), ileum, and colon, respectively. The most common endoscopic findings are multiple noduls, small polypoid lesions, white granular appearance, mucosal irregularity, erythema, ulceration, increase in wall thickness, and ulcerovegetative mass.[1,6,21,22]

Multiple lesions are detected in rates between 15% and 46.2%.[1,5-7,15-17,23-25] Furthermore, it has been shown that 85% of D-FL cases have simultaneous jejunal or ileal lesions detected by capsule or double balloon enteroscopy.[19,26]

Although abdominal pain may be prominent in some series,[15] the disease is often asymptomatic and detected incidentally.[1,6,21] In the Yamamato et al.[1] study, they examined 150 previously reported cases, noted 43.3% of the patients were asymptomaticand 28.7% with abdominal pain. In a multicenter study by Takata et al.[26] in Japan in which they summarized 125 patients with PGIFL, it was reported 76.8% of the cases were asymptomatic, and abdominal pain was 8%.

D-FL, morphologically similar to nodal FL, shows predominance of small-medium -sized cells (centrocytes) with narrow cytoplasm, indented nuclei, and no nucleoli. It contains medium- large sized cells (centroblasts) with 2-3 nucleoli with few visible cytoplasm, round nuclei, and vesicular chromatin. Neoplastic lymphoid follicles involve the mucosa and may spread to the muscularis mucosa and submucosa. Most of the lesions are low grade.[1,7,16,19,25] It is phenotypically CD20, CD10, bcl6, bcl2 positive, and CD5, CD23, CD43 negative.[1,6,11,15,20]

While the follicular dendritic cells (FDC) are pushed to the periphery in D-FL, FDC is observed scattered within the lesion in nodal follicular lymphoma with secondary gastrointestinal involvement (SGIFL).[7,11,19,27]

Our study analyzes the clinicopathological and endoscopic features of D-FL and SGIFL according to the WHO classification retrospectively.

MATERIALS AND METHODS

All NHL cases in the electronic archive were scanned retrospectively in our department between 2006 and 2022. In 919 FL cases detected among NHLs, 31 cases were diagnosed with GIFL. Demographic, clinical information, biopsy methods, and radiological (endoscopic and other imaging) results of these cases were obtained from electronic records. Macroscopic and microscopic features were recorded from the pathology reports. Pathology reports of bone marrow biopsies were also obtained.

For all biopsies, staining with hematoxylin & eosin and additional immunohistochemical (IHC) methods were prepared in our department from routinely processed formalin-fixed paraffin blocks in standard procedure. Antibodies used in IHC were CD20 [Scytek (L26)], CD3 antibody [Scytek (polyclonal)], CD5 [Scytek (4C7)], CD10 ([Biocare (56C6)], bcl6 [Biocare Medical (PF16)], bcl2 [Scytek (12 4)], CD21 [Cellmarque (2G9)], CD23 [Scytek (MHM6)], Cyclin D1 [Biocare Medical (RBT14)], Ki-67 [Dako (MIB-1)].

The localization of FL, depth of tumoral infiltration, the presence of lymphoepithelial lesions, background reactive inflammatory cells, a pattern of neoplasm (follicular, diffuse), number of centroblasts (0-5/HPF 6-15/HPF, >15/HPF) and grade (1, 2 and 3) were evaluated. All cases were reevaluated by two hematopathologists regarding their microscopic features, especially FDC patterns, according to the current WHO classification.[11-13]

In case of more than one lesion, they were classified as multiple. Patients with prominent nodal lesions and systemic disseminated at the time of diagnosis or before, were accepted as SGIFL. Staging was performed according to the Lugano classification.[4]

The study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (approval number: 2022-19/14, date: 09.12.2022). An informed consent form was not required for this study as this study is made from archive materials.

Statistical Analysis

Descriptive statistics were performed. Quantitative variables were described as median, and qualitative variables were described as percentage of each modality.

Table 1. Lugano staging system for gastrointestinal lymphomas[4]

Stage I	The tumor is confined to the GI without serosal involvement. Single primary site or multiple, non contagious lesions
Stage I-1 Stage II-2	Nodal involvement; -local (paragastric in cases of gastric lymphoma and para-intestinal for intestinal lymphoma) -distant (paraaortic, paracaval, pelvic, inguinal)
Stage IIE	Penetration of the serosa to involve adjacent organs or tissuesand peritonitis
Stage IV	Disseminated extranodal involvement, or a GI lesion with supradiaphragmatic nodal involvement

GI: Gastrointestinal tract.

RESULTS

A total of 5974 NHLs were diagnosed between 2006 and 2022, 405 (6.8%) of which were located in the GI. Thirty-one of them were GIFL. 18 (58.1%) of 31 GIFL was D-FL, and 12 (38.7%) of them were SGIFL. One case, providing insufficient data, is excluded from the study. D-FL constituted 0.3% of all NHL diagnosed in this period and 4.4% of NHL observed in the entire GI. A total of 919 FLs were detected during this period, of which D-FL constituted 1.9%.

The clinicopathological features of D-FL and SGIFL cases are summarized in Table 2, 3. The most common endoscopic and radiological findings were polyp with a rate of 61.1% in D-FL (Figure 1), and a mass with a rate of 50% in SGIFL. Polyposis was observed only in 2 (5.6%) D-FL cases located in the duodenum and gall bladder. The most common symptom was abdominal pain with 33.3% in D-FL and 58.3% in SGIFL. The most common site of the lesion was the duodenum in both groups, with rates of 44.4% in D-FL and 33.3% in SGIFL.

The immunophenotype of neoplastic cells was CD20, CD10, bcl6, bcl2 positive and CD5, CD3 and cyclin D1 negative in all D-FL and SGIFL. The Ki-67 proliferation index was between <5-30% in low grade cases and 60-85% in high grade and diffuse large B-cell lymphoma (DLBCL) transformation cases in both groups (Figure 2).

In 13 (72.2%) D-FLs, FDC was pushed to the peripher; all cases were low grade. In 1 (5.6%) case, FDC was scattered within the lesion, was high grade. In 4 (22.2%) cases, it was observed both as scattered within the lesion and pushed to the periphery (mixed pattern). Of which, 2 were low, 1 was high grade, and DLBCL transformation was observed in 1 (Table 3, Figure 3).

Table 2. Comparison of the clinical features of D-FL and SGIFL cases

Clinical features	D-FL	SGIFL
Number of cases	18	12
Gender		
Female	9 (50%)	6 (50%)
Male	9 (50%)	6 (50%)
Female/male	1/1	1/1
Mean age	56.6	53.4
Median age	60	51
Age distribution (range)	29-73	38-78
Symptom		
Abdominal pain	6 (33.3%)	7 (58.3%)
Nausea vomiting	4 (22.2%)	1 (8.3%)
B symptoms and weight loss	1 (5.6%)	2 (16.7%)
Anemia	3 (16.7%)	5 (41.6%)
GI bleeding	1 (5.6%)	-
Asymptomatic	3 (16.7%)	2 (16.7%)
Place of lesion		
Duodenum	8 (44.4%)	4 (33.3%)
Stomach	-	3 (25%) (2 corpus ,1 corpus & antrum)
Jejunum	-	-
Ileum	3 (16.7%)	3 (25%)
Ileocecal	1 (5.6%)	-
Colon	1 (5.6%)	1 (8.3%)
Gall bladder	1 (5.6%)	-
Multiple lesion	5 (27.7%)	3 (16.7%)
Duodenum and ileum	1	-
Ileum	-	1 (8.3%)
Ileum & jejunum	1	-
Ileum & large intestine	2	1 (8.3%)
Gall bladder	1	-
Stomach (corpus & antrum)	-	1 (8.3%)
- Endoscopic biopsy	14 (77.7%)	8 (66.6%)
- Right hemicolectomy after colonoscopy	1 (5.6%)	1 (8.3%)
- Partial small bowel resection	1 (5.6%)	-
- Partial small and large bowel resection	1 (5.6%)	3 (25%)
- Cholecystectomy	1 (5.6%)	-

Table 2. Continued		
Clinical features	**D-FL**	**SGIFL**
Endoscopic finding		
Polyp	11 (61.1%)	1 (8.3%)
Polyposis	2 (11.1%)	-
Nodule	1 (5.6%)	1 (8.3%)
Ulcer	2 (11.1%)	1 (8.3%)
Mass	1 (5.6%)	6 (50%)
Lymphangiectatic/infiltrating area	2 (11.1%)	-
Duodenal stenosis	-	1 (8.3%)
Wall thickening	-	2 (16.7%)
Paraaortic LAP/involvement	-	3 (25%)
Regional LAP/involvement	3 (16.7%)	5 (41.6%)
Distant LAP/involvement	-	12 (100%)
Bone marrow involvement	1 (5.6%)	3 (25%)
Liver and/or spleen involvement	-	3 (25%)
Other organs (breast, kidney, lung, pancreas)		3 (25%)
Stage		
I	14 (77.7%)	-
II (II1, II2, IIE)	3 (16.7%) (2II-1,1 II-2)	-
III	-	-
IV	1 (5.6%)	12 (100%)
GI: Gastrointestinal tract, D-FL: Duodenal follicular lymphoma, SGIFL: Nodal follicular lymphoma with secondary GI involvement, LAP: Lymphadenopathy.		

Table 3. Comparison of the pathological features of D-FL and SGIFL cases		
Pathological features	**D-FL**	**SGIFL**
Number of cases	18	12
Follicular dendritic cell network		
- pushed to the periphery	13 (72.2%) (all of them low grade)	1 (8.3%) (low grade)
- Scattered within the lesion	1 (5.6%) (high grade)	6 (50%) (3 low grade, 1 high grade, 2 DBBHL transformation)
- Mixed pattern (both scattered and pushed to the periphery)	4 (22.2%) (2 low grade, 1 high grade 1 DBBHL transformation)	5 (41.7%) (2 low grade 1 high grade 2 DBBHL transformation)
Histological grade		
Grade I	6 (33.3%)	2 (16.7%)
Grade II	1 (5.6%)	-
Grade 1-2	8 (44.4%)	4 (33.3%)
Grade IIIA ve IIIB	1 (5.6%)	2 (16.7%)
DBBHL transfromation	2 (11.1%)	4 (33.3%)
Ki67 proliferation index	**It varies between <5% and 80%**	**It varies between <5% and 85%**
Low (<5% to 30%)	15 (83.3%)	6 (50%)
High (60% to 85%)	3 (16.7%)	6 (50%)
Ulcer		
Existent	3 (16.7%) (all of them low grade)	3 (%25) (1 low grade 1 high grade 1 DBBHL transformation)
Absent	15 (83.3%) (1 high grade 1 DBBHL transformation 12 low grade)	9 (75%) (5 low grade 1 high grade 3 DBBHL transformation)

Table 3. Continued		
Pathological features	**D-FL**	**SGIFL**
Necrosis		
Existent	1 (5.6%) (DBBHL transformation)	1 (8.3%) (DBBHL transformation)
Absent	17 (94.4%)	11 (91.7%)
Inflammatory cells on the background		
Existent	1 (5.6%) (there is also ulceration on the surface)	4 (33.3%) (1 with surface ulceration, 1 with candida hyphae)
Absent	17 (94.4%)	8 (66.7%)
LEL	-	-
Pattern		
Follicular	14 (77.8%)	8 (66.7%)
Follicular & diffuse	4 (22.2%)	4 (33.3%)
IHK		
CD20 (+)	18 (100%)	12 (100%)
CD 10 (+)	18 (100%)	12 (100%)
bcl6 (+)	18 (100%)	12 (100%)
bcl2 (+)	18 (100%)	12 (100%)
CD 5 (-)	18 (100%)	12 (100%)
CD3 (-)	18 (100%)	12 (100%)
cycD1 (-)	18 (100%)	12 (100%)

GI: Gastrointestinal tract, D-FL: Dudenal follicular lymphoma, SGIFL: Nodal follicular lymphoma with secondary GI involvement, LAP: Lymphadenopathy, LEL: Lymphoepithelial lesion IHC: Immunohistochemistry.

FDC was pushed to the periphery in only 1 case (8.3%) of SGIFL, was low grade. In 6 cases (50%) that FDC was scattered within the lesion, 3 were low and 1 was high grade and DLBCL transformation was observed in 1. In 5 (41.7%) cases, mixed pattern was observed, of which 2 were low, 1 was high grade, 2 showed DLBCL transformation (Table 3, Figure 3).

DISCUSSION

The GI is the most common site for ENL and is frequently involved secondary to advanced -stage nodal NHL. PGIL is usually defined as a disease confined to the GI and regional lymph nodes, and this is usually true in cases of D-FL. Because D-FL is usually a localized disease.[1,6,7,15,16,19,21,24,25,27]

D-FL is very rare and has been increasing recently because of the widespread use of capsule endoscopy and double balloon endoscopy, and multiple biopsies taken.[5,6] D-FL accounts for 1-13%[1,6-9] of PGIL. In our study, there were 405 NHL cases located in the GI between 2006 and 2022, and a total of 31 cases were GIFL, 18 (58.1%) of which were evaluated as D-FL and 12 (38.7%) as SGIFL. In the current study, D-FL constitutes 4.4% of NHL observed in the GI.

D-FL is more common in middle-aged adults, similar to nodal FL. The median age was reported in the literature as between 56 and 62 years, while in our study it was 60.[1,6,8,15,19,26] In our D-FL cases, the median age was slightly higher compared with SGIFL (median age 51), similar to the studies of Masih et al.[27].

The female/male ratio was equal in our PGIFL and SGIFL cases. While D-FL was reported to show mild female dominance in some series[7,14,15] it was showed an equal gender distribution[6,16-20,27] in some, as in our current study.

Although D-FL can develop from any area of the GI, the rank of frequency is the duodenum (especially the 2nd part), ileum, and colon.[1,6,7,15,21,22,27] In our study, in accordance with the literature, the most common region was the duodenum in both groups with rates of 44.4% in D-FL and 33.3% in SGIFL. In D-FL, the other regions of frequency were ileum (16.7%), colon (5.6%), ileocecal region (5.6%), and gall bladder (5.6%), respectively, with rates of 25% stomach, 25% ileum, 8.3% colon in SGFIL.

While gastric location was not observed among our D-FL, all of our present 25% gastric localized cases were SGIFL. In a previous study, gastric localization was not observed among D-FL, whereas this rate was 12.5% for SGFIL.[27] The incidence of D-FL in the stomach has been reported as 4.2%[6] and 2.6%[7] in the literature.

The primary FL of the gall bladder is exceedingly rare. The age range reported is between 48-75 years and is usually low grade.[27-32] While most of them are female,[27-31] there are few males.[30,32] Multiple polyps were observed in a few reported.[30,32] Our low -grade case of FL located in the gallbladder was a 79 year old male.

Multiple lesions have been reported with a rate of 15 to 46.2%.[1,5-7,16,17,23-25,27] In the literature, the rate reaches 60%.[15] Jejunal or ileal lesions detected by capsule or double balloon enteroscopy in D-FL have been shown.[19,26] Multiple lesions were detected in 5 (27.7%) of our D-FL cases. In our multiple lesions, one was located in the duodenum and ileum, one in the ileum and jejunum, gall bladder, and the others in the ileum, large intestine.

The most common endoscopic findings are multiple nodul, small polypoid lesions in the descending part of the duodenum, white granular appearance, mucosal irregularity or erythema, ulceration, increase in wall thickness, and ulcerovegetative mass.[1,6,15,21,22,27] In accordance with

the literature, the most common endoscopic and radiological finding was polyp with a rate of 61.1% in D-FL, while in SGIFL a mass with a rate of 50%. Polyposis was observed only in 2 (5.6%) D-FL cases located in the duodenum and gall bladder.

Abdominal pain has been reported at a rate of 48-80% in studies.[15,27] In our series, the most common symptom was abdominal pain, with a rate of 33.3% in PGIFL cases and 58.3% in SGIFL cases.

The rate of asymptomatic and incidental detection has been reported as between 43.3% and 76.8%.[1,6,26] Masih et al.[27] reported the rate of asymptomatic in D-FL as 16.6% and in SGIFL as 12.5%. In our study, the rate of asymptomatic was 16.7% in both D-FL and SGIFL. The high rate observed in the study of Takata et al.[26] may be due to the high rate of endoscopy for screening asymptomatic cases in Japan.

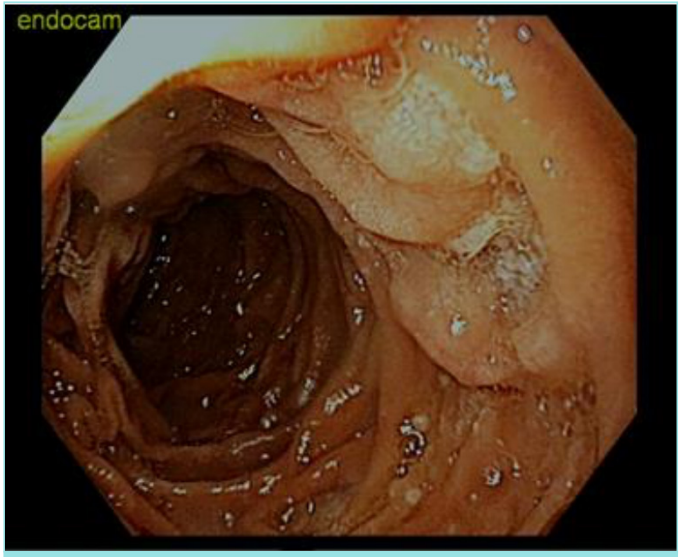

Figure 1. Polypoid lesion in the duodenum in a case with follicular lymphoma.

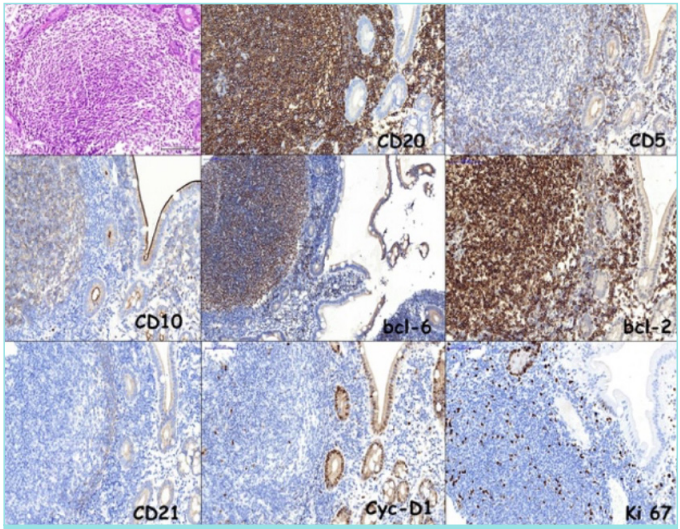

Figure 2. Follicular lymphoma in the duodenum. Presence of neoplastic lymphoid follicles, which are composed of centrocytes with small, narrow cytoplasm and irregular nuclear membrane in the small intestinal mucosa at low magnification (hematoxylin & eosin, x200); CD20 positivity (x200); CD5 negativity (x200); CD10 positivity (x200); bcl6 positivity (x200); bcl2 positivity (x200); weak follicular dendritic cells in the periphery of the neoplastic follicle with CD21 (x200); low proliferative activity observed in neoplasm with ki 67 (x200).

83.3% of our D-FL cases were low grade, this rate was reported as 80-100% in the literature.[1,6,7,15,16,19,20,25,27] 50% of our SGIFL cases were low grade. In our study, high-grade lesions was 5.6% in D-FL and 16.7% in SGIFL, and this rate was reported as 4.3% in D-FL and 20% in nodal FL.[1]

The transformation to DLBCL is uncommon, with a rate of 9.6% from D-FL to DLBCL in the literature.[6] In our study, transformation to DLBCL was observed with a rate of 11.1% in D-FL and 33.3% in SGIFL.

Phenotypically, all of our D-FL and SGIFL cases were CD20, CD10, bcl6, bcl2 positive, and CD5, CD23, and CD43 negative, in accordance with the literature.[1,6,10,11,15,20]

While FDC has been pushed to the periphery in D-FL, it has been observed scattered within the lesion in SGIFL and nodal FL.[7,11,19,27] In studies, the rate of FDC pushing to the periphery in D-FL was reported as 62% and 100%, respectively, and all of them were low grade.[19,27] Masih et al.[27] also did not observe this pattern in any of the SGIFL, whereas Misdraji et al.[7] reported that FDC was pushed to the periphery in 30.8% of the cases, the presence of a scattered pattern in 23.1%, and a mixed pattern in 30.8%. In 13 (72.2%) of our D-FL cases, FDC was pushed to the periphery, and all cases were low-grade in accordance with the literature. In 1 (5.6%) case, FDC was scattered within the lesion and this case was high grade. In 4 (22.2%) cases, a mixed pattern was observed, of which 2 were low, 1 was high grade, 2 showed DLBCL transformation. In 6 (50%) of our SGIFL cases, the FDC was scattered within the lesion. 3 of these were low grade and 1 was high grade and 2 showed DLBCL transformation. In 5 (41.7%) cases, a mixed pattern was observed, of which 2 were low, 1 was high grade, 2 showed DLBCL

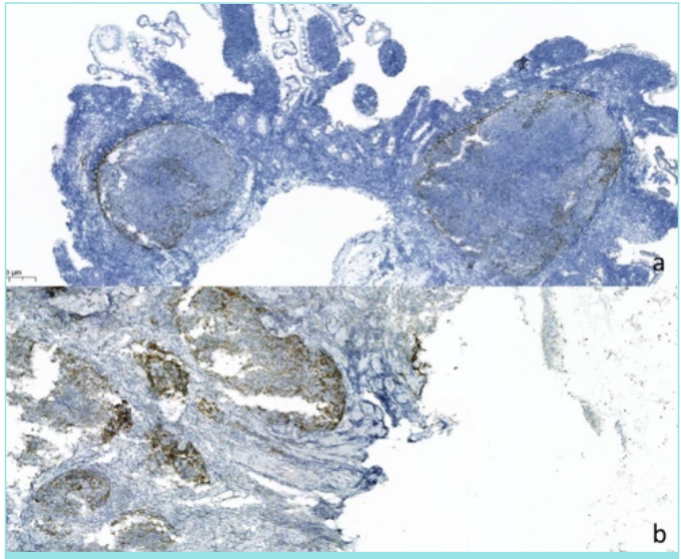

Figure 3. (a) Weak follicular dendritic cell network observed in the periphery of the neoplastic follicle with CD21 in D-FL case (x200); (b) Follicular dendritic cells, which is observed scattered in the neoplastic follicle with CD21 in a case of SGIFL (x200).

SGIFL: Nodal follicular lymphoma with secondary gastrointestinal involvement.

transformation. Only 1 (10%) FDC was pushed to the periphery and it was low grade.

D-FL cases are neoplasms progressing very slowly and tend to remain regional, mostly in the early stage (48-100% stage I).[6,7,15,16,19,24,25,27] According to the Lugano classification, 77.7% of our D-FL cases were stage I. Only 3 (16.7%) of our D-FL cases had regional lymph node involvement around the intestine and were stage II. One of the D-FL (5.6%) had bone marrow involvement and it was stage IV. In the literature, the rate of stage IV in D-FL has been reported as 5.1-16.6%.[6,7,15,20,27]

Masih et al.[27] reported that all SGIL cases had radiological paraaortic and other intraabdominal lymphadenopathy. In our study, distant lymph node involvement in all SGIFL, bone marrow in 25%, paraaortic lymph nodes in 25%, regional lymph nodes in 41.6%, liver, and/or spleen in 25%, breast, kidney, lung, and other organs such as the pancreas in 25% were detected. In 11.1% of these cases, the neoplasm exceeded the serosa and all were stage IV.

CONCLUSION

In this study, we compared the demographic, clinical, histopathological features of D-FL and SGIFL considering literature information. D-FL is follicular neoplasm in middle-aged adults, usually low grade, the most frequent involvement of the duodenum and terminal ileum, tending to remain regional, mostly early stage. The most significant difference between D-FL and SGIFL that the FDC pattern detected by CD21 and CD23 in IHC. FDC meshwork is usually pushed and restricted to the periphery of the follicul in D-FL and these are generally low grade. However, the meshwork of FDC is usually sparser and more irregularly disturbed in SGIFL and nodal FL.

MAIN POINTS

- D-FL is follicular neoplasm in middle-aged adults, usually low grade.
- D-FL is the most frequent involvement of the duodenum and terminal ileum, tending to remain regional, mostly early stage.
- The most significant difference between D-FL and SGIFL that the FDC pattern detected by CD21 and CD23 in IHC. FDC meshwork is usually pushed and restricted to the periphery of the follicul in D-FL, and these are generally low grade. However, the meshwork of FDC is usually sparser and more irregularly disturbed in SGIFL and nodal FL.

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ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (approval number: 2022-19/14, date: 09.12. 2022).

Informed Consent: An informed consent form was not required for this study as this study is made from archive materials.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.B., T.T., Design: N.B., T.T., Data Collection and/or Processing: N.B., Analysis and/or Interpretation: N.B., Literature Search: N.B., Writing: N.B.

DISCLOSURES

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

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REFERENCES

1. Yamamato S, Nakase H, Yamashita K, Matsuura M, Takada M, Kawanami C, et al. Gastrointestinal follicular lymphoma: review of the literature. J Gastroenterol. 2010; 45(4): 370-88.
2. Vannata B, Zucca E. Primary extranodal B-cell lymphoma: current concepts and treatment strategies. Chin Clin Oncol. 2015; 4(1): 10.
3. Krol AD, le Cessie S, Snijder S, Kluin-Nelemans JC, Kluin PM, Noordijk EM. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. Ann Oncol. 2003; 14(1): 131-9.
4. Rohatiner A, d'Amore F, Coiffier B, Crowther D, Gospodarowicz M, Isaacson P, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol. 1994; 5(5): 397-400.
5. Nakamura M, Ohmiya N, Hirooka Y, Miyahara R, Ando T, Watanabe O, et al. Endoscopic diagnosis of follicular lymphoma with small-bowel involvement using video capsule endoscopy and double-balloon endoscopy: a case series. Endoscopy. 2013; 45(1): 67-70.
6. Matysiak-Budnik T, Jamet P, Chapelle N, Fabiani B, Coppo P, Ruskoné-Fourmestraux A. Primary Gastrointestinal Follicular Lymphomas: A Prospective Study of 31 Patients with Long-term Follow-up Registered in the French Gastrointestinal Lymphoma Study Group (GELD) of the French Federation of Digestive Oncology (FFCD). Gut Liver. 2022; 16(2): 207-15.
7. Misdraji J, Harris NL, Hasserjian RP, Lauwers GY, Ferry JA. Primary follicular lymphoma of the gastrointestinal tract. Am J Surg Pathol. 2011; 35(9): 1255-63.
8. Fujishima F, Katsushima H, Fukuhara N, Konosu-Fukaya S, Nakamura Y, Sasano H, et al. Incidence rate, subtype frequency, and occurrence site of malignant lymphoma in the gastrointestinal tract: population-based analysis in Miyagi, Japan. Tohoku J Exp Med. 2018; 245(3): 159-65.
9. Güler B. Primary and Secondary Hematolymphoid Neoplasms of the Gastrointestinal Tract: A Single Institute Experience. Acta Oncol Turcic. 2023; 56(1): 1-12.
10. World Health Organization. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. (editors). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, IARC press; 2008.pp.220-6.
11. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. (editors). WHO classification of tumours of haematopietic and lymphoid tissues. Revised 4th ed. Lyon, France, IARC press; 2017.pp.259-90.
12. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022; 140(11): 1229-53.
13. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022; 36(7): 1720-48.
14. Yoshino T, Miyake K, Ichimura K, Mannami T, Ohara N, Hamazaki S, et al. Increased incidence of follicular lymphoma in the duodenum. Am J Surg Pathol. 2000; 24(5): 688-93.
15. Damaj G, Verkarre V, Delmer A, Solal-Celigny P, Yakoub-Aghal I, Cellier C, et al. Primary follicular lymphoma of the gastrointestinal tract: A study of 25 cases and a literature review. Ann Oncol. 2003; 14(4): 623-9.

16. Shia J, Teruya-Feldstein J, Pan D, Hegde A, Klimstra DS, Chaganti RS, et al. Primary follicular lymphoma of the gastrointestinal tract: a clinical and pathologic study of 26 cases. Am J Surg Pathol. 2002; 26(2): 216-24.

17. Sato Y, Ichimura K, Tanaka T, Takata K, Morito T, Sato H, et al. Duodenal follicular lymphomas share common characteristics with mucosa-associated lymphoid tissue lymphomas. J Clin Pathol. 2008; 61(3): 377-81.

18. Mori M, Kobayashi Y, Maeshima AM, Gotoda T, Oda I, Kagami Y, et al. The indolent course and high incidence of t(14;18) in primary duodenal follicular lymphoma. Ann Oncol. 2010; 21(7): 1500-5.

19. Schmatz AI, Streubel B, Kretschmer-Chott E, Püspök A, Jäger U, Mannhalter C, et al. Primary follicular lymphoma of the duodenum is a distinct mucosal/submucosal variant of follicular lymphoma: a retrospective study of 63 cases. J Clin Oncol. 2011; 29(11): 1445-51.

20. Saito M, Mori M, Tsukamoto S, Ishio T, Yokoyama E, Izumiyama K, et al. Duodenal-type follicular lymphoma more than 10 years after treatment intervention: A retrospective single-center analysis. World J Gastrointest Oncol. 2022; 14(8): 1552-61.

21. Iwamuro M, Kondo E, Takata K, Yoshino T, Okada H. Diagnosis of follicular lymphoma of the gastrointestinal tract: A better initial diagnostic workup. World J Gastroenterol. 2016; 22(4): 1674-83.

22. Maeshima AM, Taniguchi H, Suzuki T, Yuda S, Toyoda K, Yamauchi N, et al. Comparison of clinicopathologic characteristics of gastric follicular lymphomas and duodenal follicular lymphomas. Hum Pathol. 2017; 65: 201-8.

23. Kodama T, Ohshima K, Nomura K, Taniwaki M, Nakamura N, Kohno S, et al. Lymphomatous polyposis of the gastrointestinal tract, including mantle cell lymphoma, follicular lymphoma and mucosa-associated lymphoid tissue lymphoma. Histopathology. 2005; 47(5): 467-78.

24. Tari A, Asaoku H, Kunihiro M, Tanaka S, Fujihara M, Yoshino T. Clinical features of gastrointestinal follicular lymphoma: comparison with nodal follicular lymphoma and gastrointestinal MALT lymphoma. Digestion. 2011; 83(3): 191-7.

25. Yanai S, Nakamura S, Takeshita M, Fujita K, Hirahashi M, Kawasaki K, et al. Translocation t(14;18)/IGH-BCL2 in gastrointestinal follicular lymphoma: correlation with clinicopathologic features in 48 patients. Cancer. 2011; 117(11): 2467-77.

26. Takata K, Okada H, Ohmiya N, Nakamura S, Kitadai Y, Tari A, et al. Primary gastrointestinal follicular lymphoma involving the duodenal second portion is a distinct entity: a multicenter, retrospective analysis in Japan. Cancer Sci. 2011; 102(8): 1532-6.

27. Masih D, Chandramohan J, Sigamani E, Fouzia N A, Korula A, Simon E, et al. Comparison of primary follicular lymphoma of gastrointestinal tract and secondary involvement: A study from South India. Indian J Pathol Microbiol. 2022; 65(1): 137-41.

28. Ferluga D, Luzar B, Gadzijev EM. Follicular lymphoma of the gallbladder and extrahepatic bile ducts. Virchows Arch. 2003; 442(2): 136-40.

29. Jelic TM, Barreta TM, Yu M, Frame JN, Estallila OC, Mellen PF, et al. Primary, extranodal, follicular non-Hodgkin lymphoma of the gallbladder: Case report and a review of the literature. Leuk Lymphoma. 2004; 45(2): 381-7.

30. Mani H, Clement F, Colomo L, Pittaluga S, Raffeld M, Jaffe ES. Gall bladder and extrahepatic bile duct lymphomas: Clinicopathological observations and biological implications. Am J Surg Pathol. 2010; 34(9): 1277-86.

31. Acharya V, Ngai J, Whitelaw D, Motallebzadeh R. Primary gallbladder lymphoma presenting as a polyp. BMJ Case Rep. 2014; 2014: bcr2013202715.

32. An HJ, Lee W, Jeong CY. Primary Follicular Lymphoma of Gallbladder Presenting as Multiple Polyps. Clin Gastroenterol Hepatol. 2020; 18: e5-6.