ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 2 | Volume: 20 | Year: 2024

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 1 | Volume: 20 | Year: 2024

MEDICAL JOURNAL OF BAKIRKÖY

Medical Journal of Bakırköy of is an official scientific Journal of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (BMJ)

It is published quarterly as 4 issues every year (March, June, September, December).

Please refer to the journal's webpage **(https://bakirkoymedj.org/)** for "Ethical Policy" and "Instructions to Authors".

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The journal is published online.

Owner: University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital

Responsible Manager: Musa Çırak

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
GSM: +90 530 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing Date: June 2024
ISSN: 1305-9319 **E-ISSN:** 1305-9327
International scientific journal published quarterly.

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Editorial

Dear Colleagues,

We are great pleasure to announce that the June 2024 issue of the Medical Journal of Bakırköy has been published.

Medical Journal of Bakırköy continues its mission by publishing original research and studies in the field of general medicine. As an international journal, it will continue to develop over time with your valuable contributions. As the Editorial Team, we continue to work hard and with enthusiasm for this goal. We have full faith that we can achieve this together.

We believe that we offer you original, qualified, interesting and comprehensive articles in this June 2024 issue.

I hope you enjoy reading this issue of Medical Journal of Bakırköy. We hope that you will send your future original studies to our promising journal, along with your valuable contributions and suggestions.

Kind regards,

Musa ÇIRAK, M.D., Ph.D.
Chief Editor

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:92-96
DOI: 10.4274/BMJ.galenos.2023.2023.1-18

Research

Determinants of Conversion From Laparoscopic to Open Cholecystectomy: Türkiye Case

Laparoskopik Kolesistektomiden Açık Kolesistektomiye Geçişin Belirleyicileri: Türkiye Örneği

Hüseyin Aslan[1], Ümit Çıraklı[2], Sabri Özden[3], Emine Çetin[2]

[1]İzmir Kavram Vocational School, Healthcare Institution Management, İzmir, Türkiye

[2]İzmir Bakırçay University Faculty of Health Sciences, Department of Health Management, İzmir, Türkiye

[3]Konya City Hospital, Clinic of General Surgery, Konya, Türkiye

ABSTRACT

Objective: The aim of this study was to determine the characteristics of patients who required conversion from laparoscopic to open cholecystectomy. In addition, we compared the health outcomes of laparoscopic and converted cholecystectomy.

Methods: This was a retrospective, cross-sectional study. The laparoscopic cholecystectomy procedures performed in hospitals of the Turkish Ministry of Health in 2016 were examined. Chi-square and Mann-Whitney U tests were used to analyze the data.

Results: There were 103,387 laparoscopic cholecystectomy. Of these, 102,294 (98.9%) were laparoscopically completed, whereas 1,093 (1.1%) were converted to open cholecystectomy. The majority (75.9%) of the patients were female. The rate of conversion from laparoscopic to open cholecystectomy; in men ≥65 years of age, patients with chronic renal failure, hypertension, diabetes, malign neoplasm, and cerebrovascular disease were found to be statistically significantly higher than those in the opposing groups. Mortality, complications, intensive care unit treatment rates, and average hospitalization time were found to be statistically significant in cholecystectomy converted to open surgery.

Conclusion: Patients who had converted cholecystectomy had more negative health outcomes than those who had completed the procedure laparoscopically. Old age, being male, and having comorbidities and malignancies increase the risk of conversion to open cholecystectomy. These factors can help determine the conversion risk of laparoscopic cholecystectomy to an open procedure.

Keywords: Cholecystectomy, conversion, laparoscopic cholecystectomy, risk factors

ÖZ

Amaç: Bu çalışmanın amacı laparoskopik kolesistektomiden açık kolesistektomiye geçilmesi gereken hastaların özelliklerini belirlemektir. Ayrıca laparoskopik ve dönüştürülmüş kolesistektomilerin sağlık sonuçlarının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif, kesitsel bir çalışmadır. 2016 yılında Türkiye Cumhuriyeti Sağlık Bakanlığı hastanelerinde gerçekleştirilen laparoskopik kolesistektomi işlemleri incelenmiştir. Verilerin analizinde ki-kare ve Mann-Whitney U testleri kullanılmıştır.

Bulgular: 103.387 laparoskopik kolesistektomi yapılmıştır. Bunların 102.294'ü (98,9) laparoskopik olarak tamamlanmış, 1.093'ü (%1,1) açık kolesistektomiye çevrilmiştir. Hastaların çoğunluğu (%75,9) kadındır. Laparoskopiden açık kolesistektomiye geçiş oranının, kronik böbrek yetmezliği, hipertansiyon, diyabet, malign neoplazm ve serebrovasküler hastalığı olan erkeklerde ≥65 yaş, karşı gruplara göre istatistiksel olarak anlamlı yüksek olduğu, ölüm, komplikasyon, yoğun bakım ünitesi tedavi oranları ve ortalama hastanede kalış süresinin istatistiksel olarak anlamlı olduğu tespit edilmiştir.

Sonuç: Kolesistektomiye dönüşen hastalar, laparoskopik olarak tamamlayanlara göre daha olumsuz sağlık sonuçlarına sahip olmuştur. İleri yaş, erkek olmak, komorbidite ve malignite varlığı açık kolesistektomiye geçiş riskini artırmaktadır. Bu faktörler, laparoskopik kolesistektominin açık prosedüre dönüşme riskinin belirlenmesine yardımcı olabilir.

Anahtar Kelimeler: Kolesistektomi, konversiyon, laparoskopik kolesistektomi, risk faktörleri

Address for Correspondence: Ümit Çıraklı, İzmir Bakırçay University Faculty of Health Sciences, Department of Health Management, İzmir, Türkiye
Phone: +90 232 493 00 00 E-mail: umit.cirakli@bakircay.edu.tr ORCID ID: orcid.org/0000-0002-3134-8830

Cite as: Aslan H, Çıraklı Ü, Özden S, Çetin E. Determinants of Conversion From Laparoscopic to Open Cholecystectomy: Türkiye Case. Med J Bakirkoy 2024;20:92-96

Received: 26.01.2023
Accepted: 17.10.2023

INTRODUCTION

Cholecystectomy is a surgical procedure used in the treatment of gallstone disease. It can be performed openly and laparoscopically. Both open and laparoscopic cholecystectomy are generally safe and effective surgical procedures (1). Laparoscopic cholecystectomy is considered the "gold standard" for treating gallbladder diseases in selected patients (2-6).

Although laparoscopic cholecystectomy is often performed successfully, there is a certain rate of conversion to open cholecystectomy during the operation (7). Bleeding, internal organ injuries, adhesions, anatomical difficulties (8), inflammation, and impacted bile duct stones encountered during the operation (9) can cause the operation to be converted to open cholecystectomy (10). In the literature, it has been reported that the rate of conversion from the laparoscopic cholecystectomy procedure ranges from 3.4% to 11.4% (4,9,11-13). The surgeon's skill and patient characteristics are effective in the conversion of laparoscopic cholecystectomy to open surgery. Old age, male sex, history of upper abdominal surgery, high American Society of Anesthesiologists score, obesity, and acute cholecystitis are reported as patient-related risk factors (4,14).

Identifying patients and conditions that may require conversion to open cholecystectomy can help to select the surgical method to be performed more successfully and to take the necessary prevention measures. Thus, it may be possible to save both treatment costs and provide better quality of care. Therefore, in this study, we aimed to determine the characteristics of patients who required conversion from laparoscopic cholecystectomy to open one. In addition, we aimed to compare the health outcomes (mortality, intensive care, sepsis and hospitalization time) of converted cholecystectomy to open with those completed laparoscopically.

METHODS

This research is a retrospective, cross-sectional study. In this study, the records of laparoscopic cholecystectomy patients who underwent surgery in the hospitals of the Turkish Ministry of Health between 01.01.2016 and 31.12.2016 were retrospectively examined. Patients who underwent laparoscopic cholecystectomy were examined for the main diagnoses, gender, age, comorbidity, malignancy, length of hospital stay, intensive care use, complications, and sepsis development.

Statistical Analysis

The data of this research were obtained from the Turkish Ministry of Health. The research protocol was approved by the İzmir Bakırçay University Non-Invasive Clinical Research Ethics Board (decision no: 564, date: 20.04.2022). The SPSS Statistics 23 package program was used in the analysis. Chi-square and Mann-Whitney U tests were used to analyze the data. In the study, the confidence range was 95% and the significance value was $p<0.05\%$.

RESULTS

Within one year, 103,387 laparoscopic cholecystectomy were performed. Of these, 102,294 cases (98.9%) were laparoscopically completed, whereas 1,093 (1.1%) were converted to open cholecystectomy. The majority (75.9%) of the patients were female, younger than 65 years of age, and the average age was 50.72 years. The rate of conversion from laparoscopic to open cholecystectomy; in men, ≥65 years of age, and patients with chronic renal failure, hypertension, diabetes, malign neoplasm, and cerebrovascular disease were found to be significantly higher than those in the opposing groups (Table 1). Patients with heart disease have a higher rate of conversion to open cholecystectomy. However, this difference was not statistically significant ($p>0.05$).

Table 2 shows the comparison of health outcomes in the procedures of laparoscopically completed cholecystectomy and open cholecystectomy. According to the results of the analysis, mortality, complications, intensive care unit treatment rates, and average hospitalization time were found to be statistically significant in cholecystectomy converted to open surgery. However, the rate of development of sepsis was not statistically significant ($p<0.05$).

A comparison of mortality rates according to patient characteristics is given in Table 3. Although the share of male patients in the total patient was approximately 1/4, the mortality rate was found to be higher than that of women. It was found that mortality rates were higher in patient groups diagnosed with hypertension, diabetes, and sepsis and in patient groups aged 65 and over who were converted from laparoscopic cholecystectomy to open cholecystectomy compared with their counterparts. In addition, although data did not meet the requirements for chi-square analysis, mortality rates were higher in patients with heart disease, cerebrovascular disease, chronic renal failure, and malignancies.

DISCUSSION

Conversion of laparoscopic cholecystectomy to open cholecystectomy results in negative health outcomes and additional costs. Therefore, in this study, the rates and causes of conversion of laparoscopic cholecystectomy to open cholecystectomy were investigated. In previous studies, the

Table 1. Comparison of patient groups according to type of cholecystectomy

Characteristic		Laparoscopic (n/%)	Converted to open (n/%)	Total (n)	p-value
Sex	Male	24,376/97.9	519/2.1	24,895	<0.001*
	Female	77,918/99.3	574/0.7	78,492	
Age	<65	84,315/99.1	766/0.9	85,081	<0.001*
	≥65	17,979/98.2	327/1.8	18,306	
Chronic renal failure	No	102,152/98.9	1,084/1.1	103,236	<0.001*
	Yes	142/94.0	9/06	151	
Heart disease	No	101,673/98.9	1,082/1.1	102,755	0.092
	Yes	621/98.3	11/1.7	632	
Hypertension	No	96,116/99.0	995/1.0	97,111	<0.001*
	Yes	6,178/98.4	98/1.6	6,276	
Diabetes	No	95,513/99.0	960/1.0	96,473	<0.001*
	Yes	6,781/98.1	133/1.9	6,914	
Malignant neoplasm	No	102,140/99.0	1,079/1.0	103,219	<0.001*
	Yes	154/91.7	14/8.3	168	
Cerebrovascular diseases	No	102,219/98.9	1,090/1.1	103,309	0.016*
	Yes	75/96.2	3/3.8	78	
Total		102,294/98.9	1,093/1.1	103,387	

*p<0.05

Table 2. Health output of patients according to type of cholecystectomy

		Laparoscopic	Converted to open	Total	p-value
Mortality	No	102,231/99.0	1,084/1.0	103,315	<0.001*
	Yes	63/87.5	9/12.5	72	
Complication	No	101,902/99.1	976/0.9	102,878	<0.001*
	Yes	392/77.0	117/23.0	509	
Sepsis	No	102,274/98.9	1,092/1.1	103,366	<0.001
	Yes	20/95.2	1/4.8	21	
Intensive care	No	99,749/99.0	963/1.0	100,712	<0.001*
	Yes	2,545/95.1	130/4.9	2,675	
Hospital length of stay (mean ± SD[a])		4.20±2.401	7.07±4.153	4.23±2.444	<0.001*
Total		102,294	1,093	103,387	

*p<0.05, SD: Standard deviation

rates and causes of conversion to open cholecystectomy have varied. This study is considered important because it is the first comprehensive study in Türkiye and evaluates all procedures performed in hospitals affiliated with the Turkish Ministry of Health for a full year.

The rates of conversion of laparoscopic cholecystectomy to open cholecystectomy vary according to the studies. The rates of conversion of laparoscopic cholecystectomy to open cholecystectomy range from 07% to 9.5% (4,8,11,12,15-20). In this study, the conversion rate of laparoscopic cholecystectomy to open cholecystectomy was 1.1%. Compared with the studies in the literature, except for two studies, it is possible to say that this conversion rate is low.

The conversion rate of laparoscopic cholecystectomy to open cholecystectomy is affected by patient-related factors. In this study, it was found that the conversion rate was higher (three times) in male patients (2.1%) than in women (0.7%). The findings of our study are in accordance with the findings of previous studies (4,9,12,19,20). It has also been confirmed by both systematic reviews and meta-analyses that male sex is a risk factor for conversion to open cholecystectomy (14).

Table 3. Comparison of mortality rates according to patients' characteristics

		Mortality No	Mortality Yes	Total	p-value
		(n/%)	(n/%)		
Sex	Male	24,864/99.88	31/0.12	24,895	<0.001*
	Female	78,451/99.95	41/0.05	78,492	
Age	<65	85,063/99.98	18/0.02	85,081	<0.001*
	≥65	18,252/99.71	54/0.29	18,306	
Laparoscopic cholecystectomy		102,231/99.94	63/0.06	102,294	<0.001*
Laparoscopic converted to open		1,084/99.18	9/0.82	1,093	
Malignant neoplasm	No	103,266/99.93	69/0.07	103,335	-
	Yes	49/94.23	3/5.77	52	
Complication	No	102,820/99.94	58/0.06	102,878	<0.001*
	Yes	495/97.25	14/2.75	509	
Sepsis	No	103,305/99.94	61/0.06	103,366	<0.001*
	Yes	10/47.62	11/52.38	21	
Hypertension	No	97,059/99.95	52/0.05	97,111	<0.001*
	Yes	6,256/99.68	20/0.32	6,276	
Diabetes	No	96,415/99.94	58/0.06	96,473	<0.001*
	Yes	6,900/99.80	14/0.20	6914	
Heart disease	No	102,688/99.93	67/0.07	102,755	-
	Yes	627/99.21	5/0.79	632	
Cerebrovascular diseases	No	103,241/99.93	68/0.07	103,309	-
	Yes	74/94.87	4/5.13	78	
Chronic renal failure	No	103,167/99.93	69/0.07	103,236	-
	Yes	148/98.01	3/1.99	151	
Total		103,315/99.93	72/0.07	103,387	-

*p<0.05

Age is a factor frequently examined in the conversion from laparoscopic cholecystectomy to open cholecystectomy. Previous studies have also found that old age is a risk factor for conversion to open cholecystectomy (4,9,10,12,14,16,19,20). In the study, patient ages were examined as <65 and ≥65. In our study, a statistically significant difference was found in male patients over 65 years of age.

In this study, it was found that the rates of conversion to open cholecystectomy were higher in patients with heart disease, hypertension, diabetes, cerebrovascular disease, and malignant neoplasms and in patients with complications. Lipman et al. (17) reported a higher rate of conversion from laparoscopic cholecystectomy to open surgery in patients with diabetes and heart failure, and other studies (10,21) reported a higher conversion rate in patients with hypertension. In our study, malignancy was detected during or after surgery because of pathology. Out of 168 patients with malignancy identification, 14 (8.3%) converted to open surgery, and the operations of 154 patients were completed laparoscopically. In another study (21), malignancy was also found to be a risk factor.

The main reason for the preference of the laparoscopic approach in cholecystectomy is the low risk and comfort it provides to patients. For this purpose, health outcomes were examined in patients who converted from laparoscopy to open surgery. Mortality, complications, sepsis, the need for intensive care treatment, and hospital stay were examined as health outcomes. Of the health outcomes examined, all factors except sepsis were found to be significantly higher in patients who converted to open surgery. Similarly, other studies (1,4,11-13) have also found that mortality rate and length of hospital stay (10,12,21) were higher in the operations converted to open surgery than in those completed laparoscopically. Navez et al. (12) found a high complication rate in the converted operations.

There are some limitations to this study. First, the study is a registry survey, and the data are assumed to be correct.

Another limitation is that only the hospital data of the Ministry of Health of Türkiye could be examined during the research period, and the data of the procedures performed in university hospitals and private hospitals could not be obtained.

CONCLUSION

Although conversion to open surgery is not considered a failure, patients with conversion have more negative health outcomes than those completed laparoscopically. Mortality, the risk of complications, the rate of receiving intensive care treatment, and hospital stay are increasing in patients who have undergone open cholecystectomy.

Although it is inevitable that a certain rate of laparoscopic cholecystectomy will convert to open surgery, it is possible to reduce the conversion rate with a better preoperative evaluation. It is important to determine the risk factors in the preoperative evaluation. Old age, being male, and having comorbidities and malignancies increase the risk of conversion to open cholecystectomy. In these patients, preoperative evaluation should be performed more carefully, and it is useful to prepare the operation considering the possibility of conversion to open surgery.

ETHICS

Ethics Committee Approval: The study was approved by İzmir Bakırçay University University Non-Invasive Clinical Research Ethics Board with its decision dated 20 April 2022 and numbered 564.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.Ç.A., Concept: H.A., S.Ö., Design: H.A., S.Ö., Data Collection or Processing: Ü.Ç., E.Ç.A., Analysis or Interpretation: Ü.Ç., Literature Search: H.A., Ü.Ç., S.Ö., E.Ç.A., Writing: H.A., Ü.Ç., S.Ö., E.Ç.A.

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

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

REFERENCES

1. Wolf AS, Nijsse BA, Sokal SM, Chang Y, Berger DL. Surgical outcomes of open cholecystectomy in the laparoscopic era. Am J Surg 2009;197:781-4.
2. Bingener-Casey J, Richards ML, Strodel WE, Schwesinger WH, Sirinek KR. Reasons for conversion from laparoscopic to open cholecystectomy: a 10-year review. J Gastrointest Surg 2002;6:800-5.
3. Bittner R. The standard of laparoscopic cholecystectomy. Langenbecks Arch Surg 2004;389:157-63.
4. Harboe KM, Bardram L. The quality of cholecystectomy in Denmark: outcome and risk factors for 20,307 patients from the national database. Surg Endosc 2011;25:1630-41.
5. Lill S, Rantala A, Vahlberg T, Grönroos JM. Elective laparoscopic cholecystectomy: the effect of age on conversions, complications and long-term results. Dig Surg 2011;28:205-9.
6. Sidhu RS, Raj PK, Treat RC, Scarcipino MA, Tarr SM. Obesity as a factor in laparoscopic cholecystectomy. Surg Endosc 2007;21:774-6.
7. Peters JH, Krailadsiri W, Incarbone R, Bremner CG, Froes E, Ireland AP, et al. Reasons for conversion from laparoscopic to open cholecystectomy in an urban teaching hospital. Am J Surg 1994;168:555-8.
8. Le VH, Smith DE, Johnson BL. Conversion of laparoscopic to open cholecystectomy in the current era of laparoscopic surgery. Am Surg 2012;78:1392-5.
9. Sutcliffe RP, Hollyman M, Hodson J, Bonney G, Vohra RS, Griffiths EA, et al. Preoperative risk factors for conversion from laparoscopic to open cholecystectomy: a validated risk score derived from a prospective U.K. database of 8820 patients. HPB (Oxford) 2016;18:922-8.
10. Tayeb M, Raza SA, Khan MR, Azami R. Conversion from laparoscopic to open cholecystectomy: multivariate analysis of preoperative risk factors. J Postgrad Med 2005;51:17-20.
11. Csikesz N, Ricciardi R, Tseng JF, Shah SA. Current status of surgical management of acute cholecystitis in the United States. World J Surg 2008;32:2230-6.
12. Navez B, Ungureanu F, Michiels M, Claeys D, Muysoms F, Hubert C, et al. Surgical management of acute cholecystitis: results of a 2-year prospective multicenter survey in Belgium. Surg Endosc 2012;26:2436-45.
13. Wiseman JT, Sharuk MN, Singla A, Cahan M, Litwin DE, Tseng JF, et al. Surgical management of acute cholecystitis at a tertiary care center in the modern era. Arch Surg 2010;145:439-44.
14. Philip Rothman J, Burcharth J, Pommergaard HC, Viereck S, Rosenberg J. Preoperative Risk Factors for Conversion of Laparoscopic Cholecystectomy to Open Surgery - A Systematic Review and Meta-Analysis of Observational Studies. Dig Surg 2016;33:414-23.
15. Ekici U, Tatlı F, Kanliöz M, İnan T. Leukocytosis can predict the increased risk of conversion in elective laparoscopic cholecystectomy. Laparosc Endosc Surg Sci 2017;24:81-4.
16. Kama NA, Kologlu M, Doganay M, Reis E, Atli M, Dolapci M. A risk score for conversion from laparoscopic to open cholecystectomy. Am J Surg 2001;181:520-5.
17. Lipman JM, Claridge JA, Haridas M, Martin MD, Yao DC, Grimes KL, et al. Preoperative findings predict conversion from laparoscopic to open cholecystectomy. Surgery 2007;142:556-63.
18. Nassar AHM, Zanati HE, Ng HJ, Khan KS, Wood C. Open conversion in laparoscopic cholecystectomy and bile duct exploration: subspecialisation safely reduces the conversion rates. Surg Endosc 2022;36:550-8.
19. Rosen M, Brody F, Ponsky J. Predictive factors for conversion of laparoscopic cholecystectomy. Am J Surg 2002;184:254-8.
20. Simopoulos C, Botaitis S, Polychronidis A, Tripsianis G, Karayiannakis AJ. Risk factors for conversion of laparoscopic cholecystectomy to open cholecystectomy. Surg Endosc 2005;19:905-9.
21. Livingston EH, Rege RV. A nationwide study of conversion from laparoscopic to open cholecystectomy. Am J Surg 2004;188:205-11.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:97-103
DOI: 10.4274/BMJ.galenos.2023.2023.3-2

Research

Examining the Quality of Life and Healthy Lifestyle Behaviour Before and After Bariatric Surgery

Obezite Cerrahisi Öncesi ve Sonrası Yaşam Kalitesi ve Sağlıklı Yaşam Biçimi Davranışlarının İncelenmesi

Duygu Ateş[1], Hatice Yorulmaz[1], Elif Yorulmaz[2], Bora Koç[3]

[1]Haliç University Faculty of Health Sciences, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Bağcılar Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Türkiye

[3]Medicana Hospital, Clinic of Obesity and Metabolism Surgery, İstanbul, Türkiye

ABSTRACT

Objective: In this study, we aimed to examine the impact of healthy lifestyle behavior and quality of life scale of patients undergoing bariatric surgery and their demographic and disease-related features before and after bariatric surgery.

Methods: The research was completed with a total of 33 patients who had undergone bariatric surgery, and it was carried out according to the descriptive cross-sectional research in İstanbul. The data were collected using the Descriptive Information form, Healthy Lifestyle Behaviour, and Quality of Life scales.

Results: Of the patients, 75.8% were female, and their mean age was 37.9±13.1 years. Of the patients, 27.2% had sexual problems before operation, 6% had quite sexual problems after operation, had no limitation of movement after operation, 78.7% before operation were 3rd class obese, and 15.2% were found to be 3rd grade obese. It was observed that the physical and mental main scores of the quality of life scale and the total score of the healthy lifestyle behaviors scale increased significantly after the operation compared with the pre-operative period ($p<0.05$).

Conclusion: The body mass indexes of the patients decreased after the operation, and the symptoms of the disease and sexual problems decreased. In the study, it was concluded that the reduction of body weight provided by bariatric surgery is effective in increasing the quality of life of patients.

Keywords: Bariatric surgery, healthy lifestyle behaviour, quality of life

ÖZ

Amaç: Çalışma obezite cerrahisi uygulan hastalarda, demografik ve hastalığa ilişkin özellikleri sağlıklı yaşam biçimi davranışları ve yaşam kalitesine operasyon öncesi ve sonrasında oluşan etkilerini belirlemek amacıyla yapıldı.

Gereç ve Yöntem: Çalışma; obezite cerrahisi uygulanan toplam 33 hasta ile tanımlayıcı kesitsel araştırma tipine göre İstanbul ilinde gerçekleştirildi. Veriler Tanıtıcı Bilgi formu, Sağlıklı Yaşam Biçimi Davranışları ve Yaşam Kalitesi ölçekleri kullanılarak toplandı.

Bulgular: Araştırmaya katılan hastaların, %75,8'i kadın, ve yaş ortalamaları 37,9±13,1'dir. Hastaların operasyon öncesi %27,2'sinin oldukça cinsel sorun yaşadığı sonrasında ise, %6'sının oldukça cinsel sorun yaşadığı, operasyon sonrasında hareket kısıtlılığı yaşamadıkları, öncesi %78,7'sinin 3. sınıf obez, sonrası %15,2'sinin 3. sınıf obez olduğu saptandı. Hastaların, operasyon sonrasında operasyon öncesine göre yaşam kalitesi ölçeği fiziksel ve mental ana skor puanlarının ve sağlıklı yaşam biçimi davranışları ölçeği toplam puanının anlamlı ölçüde arttığı görüldü ($p<0,05$).

Sonuç: Hastaların operasyon sonrasında vücut kitle indekslerinin azaldığı, hastalık semptomları ve seksüel problemlerinin azaldığı görüldü. Çalışmada, bariatrik cerrahinin sağladığı vücut ağırlığının azalmasının hastaların yaşam kalitesini artırmada etkili olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Obezite cerrahisi, sağlıklı yaşam biçimi davranışları, yaşam kalitesi

Address for Correspondence: Hatice Yorulmaz, Haliç University Faculty of Health Sciences, İstanbul, Türkiye
Phone: +90 212 924 24 44 E-mail: haticeyorulmaz@halic.edu.tr ORCID ID: orcid.org/0000-0002-0550-9899

Cite as: Ateş D, Yorulmaz H, Yorulmaz E, Koç B. Examining the Quality of Life and Healthy Lifestyle Behaviour Before and After Bariatric Surgery. Med J Bakirkoy 2024;20:97-103

Received: 23.03.2023
Accepted: 24.07.2023

INTRODUCTION

Obesity is a complex disease characterized by an abnormal or excessive amount of body fat (1). Obesity appears to be an increasing problem in Türkiye and in developed countries. The main reasons for the increase in obesity prevalence are, especially with the developing technology in transportation, entertainment, production, and agriculture sectors, the decrease in physical activity secondary to the facilitation of the lifestyle and the increase in energy intake because of the rapid change in dietary habits.

According to the World Health Organization (WHO) report (2022), 59% of adults in the European region reported that one-third of every child complained of being overweight or obese. Data have shown that it increases obesity rates in the coronavirus disease-2019 pandemic. The prevalence of obesity in the adult population in Türkiye exceeds 30%. Although the prevalence of obesity is higher in women, the recent rapid increase in male obesity is also noteworthy. According to the WHO European Region, according to the Obesity Report 2022. It has been reported that the country with the highest prevalence of obesity is Türkiye in the European. In Türkiye, 66.8% of the adult population is overweight and 32.1% is obese (2,3). The fact that obesity is such a significant problem and has a high prevalence makes both obese individuals and experts in search of treatment. In obesity treatment, surgical methods including new techniques and diet, exercise, medicine, and similar methods have been started to be used. When the reason directing obese individuals to surgery is examined, it is observed that a great majority of the obese and overweight individuals are not ready for the treatment programs that may get their weight under control and provide continuance of their diets or cannot maintain their treatment, many of them are deprive of the exercise programs and the behavioral change therapies and the psychological problems that have a significant effect on eating behaviors are not treated (4,5).

The daily lives, physical activities, and sleep quality of obese individuals are significantly affected. Obesity affects the social and psychological balance of the individual negatively by causing them to stay away from social life (6). It has been reported that recovery has been observed in the quality of life (QOL) and mental health after bariatric surgery (7). Individuals with high QOL maintain their lives independently and meet their requirements and daily life activities. It has been reported that individuals with healthy lifestyle behaviors have a high QOL and display health preventive and promotion behaviors more easily (8). This study aimed to examine the effect of surgical operation on healthy lifestyle behaviors and QOL in Turkish patients who underwent bariatric surgery.

METHODS

The study was conducted with 33 Turkish patients who were willing to participate in the study, among 51 patients who applied to a Private Clinic in İstanbul for bariatric surgery after the approval of the Haliç University Non-invasive Clinical Research Ethics Committee was received (decision no: 3, date: 24.10.2018). All patients were informed about the study, and written informed consent was obtained for the protocol. This was a descriptive and cross-sectional study. Laparoscopic Roux-en-Gastric bypass was performed in the patients. The research was conducted using face-to-face interview technique in the pre-operative period and at the 6th month postoperative follow-up. The introductory information form, including personal characteristics and disease-related information in the pre-operative period and in the postoperative 6th month, "Healthy Lifestyle Behaviours" scale and "SF-36 Quality of Life" questionnaire were used in the study to collect the data.

Introductory Information Form

The introductory information form includes questions for determining age, gender, marital status, educational level, pre-operative and postoperative body mass index (BMI), profession, family history of the disease, duration of the disease, smoking use, chronic illness (i.e., hypertension, diabetes,.), receiving psychological support, pre-operative and postoperative problems, and pre-operative and postoperative sexual behaviors. Weight and height measurements of each patient were recorded to measure BMI using the standard BMI formula (kg/height^2). Persons with BMIs between 18.5 and 24.9 were considered to have normal weight and were included in the first group. The second group comprised persons who presented BMIs between 30.0 and 39.9, which are considered degrees I and II of obesity. The obesity third group was composed of BMI greater than or equal to 40 (9).

Healthy Lifestyle Behaviours Scale

The Health Promoting Lifestyle Measurement Instrument was advanced by Walker et al. (10) (1987) and derived from the health promotion model of Pender to measure the health promotion behaviors of individuals. The Turkish validity and reliability study of the Healthy Lifestyle Behaviours scale was conducted by Bahar et al. (11). The scale is composed of 52 items and six factors. These include spiritual growth, interpersonal relations, nutrition, physical activity, health responsibility, and stress management. The scale is rated

and scored as never (1) and regularly (4). The lowest possible score is 52, and the highest score is 208.

SF-36 Quality of Life Questionnaire

The Short Form-36 (SF-36) QOL questionnaire was developed by Ware (12) to assess the QOL. The Turkish validity and reliability study of SF-36 was conducted by Koçyiğit et al. (13). The questionnaire consists of 36 items and measures 8 dimensions of health: physical functionality (10 items), social functioning (2 items), role limits due to physical problems (4 items), role limits due to emotional problems. problems (3 items), mental health (5 items), energy/vitality (4 items), pain (2 items), and general health perception (5 items). It assesses health between 0 and 100 with the subscales. There is no total scoring calculation. Zero points signify bad health and 100 points signify well-being. The weighted sum of the scores of the questions, including the subscales of the SF-36 QOL scale, is calculated so that the physical and mental health summary score is obtained.

Statistical Analysis

The assessment of the data was performed using IBM SPSS Statistics 22 software. To assess the conformity of the data to the normal distribution, the Kolmogorov-Smirnov test was used. Descriptive statistics (mean, standard deviation, percentage, frequency), paired t-test, and Pearson's correlation test were used for normally distributed data. The data were examined at a significance level of $p<0.05$.

RESULTS

It was detected that 39.3% of the patients were between the ages of 19 and 30 years, 75.8% were female, 57.5% had graduate and postgraduate education, and 66.7% were employed. (Table 1). It was determined that there were obese people in the families of 54.5% of the participants, 63.6% had a weight problem for 4-21 years, 60.6% had an additional disease, 33.3% of the patients were smoker before the operation, 18.2% reduced smoking after the operation, 21.2% had psychological support, all of them stopped having psychological support after the operation, and when the BMI values were examined before the operation, it was observed that 78.7% of them were class 3 obese and 57.5% were class I obese after the operation. It was observed that 36.4% of the patients had shortness of breath before the operation, 27.3% had joint pains, 39.4% had social isolation, 51.5% had a limitation of movement, and they did not experience these problems after the operation. It was determined that 57.6% of them did not experience any sexual problem before the operation and 84.8% did not have any sexual problem after the operation, 24.2% of them felt that they lost sexual attraction before the operation, 21.2% felt that their sexual drive reduced/disappeared and after the operation, 6.1% of them felt that they lost sexual attraction, and 9.1% felt that their sexual desire reduced/disappeared (Table 2).

It was observed that the main dimension of healthy lifestyle behaviors and the QOL questionnaire subscale and total scores of the patients increased at a statistically significant level in the postoperative period compared with the pre-operative period ($p<0.01$) (Table 3). When the scores of the patients taken from the subscales of the healthy lifestyle behaviors scale in the preoperative and postoperative periods were examined, it was observed that they had higher scores from all the subscales of the scale in the postoperative period compared with the pre-operative period ($p<0.01$) (Table 4). Before the operation, a positive moderate correlation was found between the score of healthy lifestyle behaviors and the physical main dimension of the QOL questionnaire ($r=0.41$; $p<0.05$) and a positive moderate significant correlation was found between the score of healthy lifestyle behaviors and the mental main dimension ($r=0.42$; $p<0.05$). After the operation, a positive moderate significant correlation was found between the

Table 1. The sociodemographic characteristics of the patients (n=33)

Variable	Variable categories	Number	Percentage
Age	19-30	13	39.3
	31-50	15	45.5
	51-67	5	15.2
Gender	Female	25	75.8
	Male	8	24.2
Marital status	Married	17	51.5
	Single	16	48.5
Educational status	Primary education	5	15.2
	High school	9	27.3
	Graduate and postgraduate	19	57.5
Employment status	Employed	22	66.7
	Unemployed	11	33.3
The presence of obese family member	Yes	18	54.5
	No	15	45.5
The duration of weight problem	4-21 years	21	63.6
	22-39 years	10	30.3
	40-56 years	2	6.1
Chronic illness (i.e., hypertension, diabetes, ...)	Yes	20	60.6
	No	13	39.4

Table 2. The disease-related characteristics of the patients (n=33)

Variable	Before operation		Variable	After operation	
	Number	Percentage		Number	Percentage
Smoking					
Yes	11	33.3	Decreased	6	18.2
No	17	51.5	Increased	1	3.0
Quitting	5	15.2	Same	26	78.8
Psychological support					
Yes	7	21.2	Yes	-	-
No	26	78.8	No	33	100
BMI					
Class I obese	2	6.1	Normal weight	2	6.1
Class II obese	5	15.2	Class I obese	19	57.5
Class III obese	26	78.7	Class II obese	7	21.2
	-	-	Class III obese	5	15.2
Problems of the patients*					
Shortness of breath	12	36.4	Shortness of breath	-	-
Joint pains	9	27.3	Joint pains	-	-
Social isolation	13	39.4	Social isolation	-	-
Limitation of movement	17	51.5	Limitation of movement	-	-
Sexual problems					
Never	19	57.6	Never	28	84.8
Little	5	15.2	Little	3	9.2
Quite	9	27.2	Quite	2	6.0
The reasons for preoperative sexual problems*					
The feeling of losing sexual attraction	8	24.2	The feeling of losing sexual attraction	2	6.1
The feeling of decreasing/losing sexual desire	7	21.2	The feeling of decreasing/losing sexual desire	3	9.1
The attitude of the partner	2	6.1	The attitude of the partner	2	6.1
Positional difficulty	3	9.1	Positional difficulty	-	-
Failing to tolerate effort	2	6.1	Failing to tolerate effort	2	6.1

*More than one answer was given, BMI: Body mass index

score of healthy lifestyle behaviors and the physical main dimension of the QOL questionnaire (r=0.37; p<0.05) and a positive moderate significant correlation was found between the score of healthy lifestyle behaviors and the mental main dimension (r=0.40; p<0.05) (data not shown in the table).

DISCUSSION

In obesity treatment, bariatric surgery, as well as diet, exercise, medicine, and traditional methods, is one of the methods used recently to recover, recover completely related to the other problems caused by obesity and to prevent the emergence of new problems caused by obesity (4). In addition to weight loss, metabolic and bariatric surgery leads to clinically significant improvements in obesity-related complications, cardiometabolic risk factors, musculoskeletal pain, and functional mobility (14).

It was observed that the main dimension of the QOL questionnaire and all subscales and total scores of the healthy lifestyle behaviors scale increased in the patients in the postoperative period. In addition, a positive significant moderate correlation was found between healthy lifestyle behaviors and the QOL questionnaire. Ustundag et al. (15) obtained similar results in their study. In another study, it was determined that obese individuals had higher scores on the healthy lifestyle behaviors scale after the operation compared with healthy individuals (16). In the study of Yaralı et al. (17) the mean healthy lifestyle behaviors scale total score of the patients who had bariatric surgery was found to be moderate. de Zwaan (18) showed results on QOL assessed based on the SF-36 questionnaire in the group of patients operated on with bariatric surgery only. Similar to our study, the

Table 3. The findings on the quality of life questionnaire overall and subscale scores of the patients before and after the operation (n=33)

Main dimensions and subscales	Before the operation		After the operation		t	p-value
	Mean	Standard deviation	Mean	Standard deviation		
Physical functioning	17.61	5.70	28.36	2.35	11.43	0.00**
Social functioning	6.06	2.39	9.09	1.07	7.20	0.00**
Physical role	5.09	1.60	7.48	1.00	7.86	0.00**
Mental role	4.21	1.29	5.89	1.94	4.04	0.00**
Mental health	15.55	4.92	24.45	3.88	8.94	0.00**
Vitality	11.24	4.54	18.97	4.05	7.89	0.00**
Pain	6.54	2.80	9.96	2.04	6.99	0.00**
General health perception	11.76	4.09	20.68	3.15	10.67	0.00**
Physical main dimension	40.99	9.70	66.48	6.33	14.14	0.00**
Mental main dimension	37.06	11.53	58.40	8.29	9.27	0.00**

**p<0.01, t: Paired t-test value

Table 4. The findings on the healthy lifestyle behaviours scale subscale scores of the patients before and after the operation (n=33)

Subscales	Before the operation		After the operation		t	p
	Mean	Standard deviation	Mean	Standard deviation		
Spiritual growth	24.27	5.03	29.97	3.73	6.86	0.00**
Health responsibility	18.21	4.76	23.24	5.14	6.01	0.00**
Physical activity	14.18	5.34	22.24	4.81	7.84	0.00**
Nutrition	19.27	4.07	23.48	3.75	6.79	0.00**
Interpersonal relations	25.39	4.72	28.61	4.44	5.06	0.00**
Stress management	17.97	3.26	21.97	3.97	6.54	0.00**
Total score	119.30	19.68	149.52	18.27	8.84	0.00**

**: p<0.01, t: Paired t-test value

author observed a significant improvement in all studied parameters (18).

It was determined that the patients undergoing bariatric surgery were mainly female. All over the world, the prevalence of obesity is higher in women. The reason for this is that women store fatter (19). It has been determined that the prevalence of obesity is 29.9% in women and 12.9% in men (20). It was observed that the patients undergoing bariatric surgery were mostly married and most of them were employed. All of the unemployed patients were housewives (19). Beyond weight loss, the benefit of bariatric surgery is also improved QOL for patients, as shown by the present study 2 years after surgery (21). Pirinçci et al. (22) showed that housewives were more obese than other occupations.

It was found that the patients undergoing bariatric surgery were mostly in the age group of 31-50 years. Ustu et al. (23) showed that among Turkish adults, obesity is positively associated with age. In the study by Loux et al. (24) it was determined that there was an enhancement in the QOL in young patients after bariatric surgery.

It was detected that 15.2% of the patients undergoing bariatric surgery were in the primary school group, 27.3% in the high school group, and 57.5% in the graduate and postgraduate group. The increasing educational level of the individuals may prompt them to seek new solutions, and this positively affects the adaptation period after bariatric surgery to be maintained and managed more consciously.

It was shown that 54.5% of the patients participating in the study had an obese family member. In another study, it was determined that most of the individuals had overweight parents and that there were other overweight individuals in their families (25). When the genetic factors causing the formation of obesity are examined, it has been determined that children with obese parents or children raised away from their biological parents tend to be obese. In particular, in studies with adopted children, it was observed that the BMI of the children was more similar to that of their biological parents (26).

When the duration of the weight problem of the patients in the sample group was examined, it was found that 63.6% of them had a weight problem for 4-21 years, 30.3% had this problem for 22-39 years, and 6.1% had this problem for 40-56 years. As the duration of the weight problem increased, they accepted this situation, and accordingly their adaptation process and life conditions were shaped.

It was observed that 21.2% of the patients had psychological support and 78.8% did not. It was determined that the patients who had psychological support did not need psychological support in the postoperative period. Obese women were found to be more depressed than normal women, and there was a significant relationship between BMI and depression (22). In the study by Wimmelmann et al. (7), it was observed that the psychiatric symptoms decreased after bariatric surgery similar to the improvement of inappropriate eating behaviors of the patients.

When the pre-operative BMI values of the patients were examined, it was observed that 6.1% of them were class I obese, 15.2% of them were class II obese, and 78.7% were class III obese. When their postoperative BMI values were examined, it was determined that 6.1% of them had normal weight, 24.2% were pre-obese, 57.5% were class I obese, 21.2% were class II obese, and 15.2% were class III obese. When the pre-operative and postoperative BMI values of the patients were examined, it was determined that the QOL and healthy lifestyle behaviors of all the groups were positively affected after the operation. A significant decrease was observed in the BMI values of patients who underwent vertical banded gastroplasty (27).

In our study, 60.6% of the patients were found to have an additional chronic disease. Kuyucu (2018) (28) determined that 56.7% of the individuals had an additional disease before the operation (diabetes, hypertension etc.). Zhang et al. (29) showed that insulin resistance improved 3 months after surgery in 37 obese patients who underwent laparoscopic sleeve gastrectomy.

It was found that before the operation, 36.4% of the patients had shortness of breath, 27.3% had joint pains, 39.4% had social isolation, and 51.5% had a limitation of movement. It was observed that after the operation, 12.1% of the patients had nausea and vomiting, 9.1% had pain in the wound site, and 15.2% had weakness. It was determined that the patients did not have the problems that they had before the operation or after the operation. In another study showed that weight loss associated with bariatric surgery improves dyspnea in daily living (30).

Psychosocial problems such as dissatisfaction with body images, unhappiness in marriages, and difficulties in sexual life are more frequent in obese people (31). When the condition of having sexual problems before and after the operation was examined, it was determined that 57.6% of the patients did not have any sexual problems before the operation, 15.2% had little sexual problems, and 27.5% had any significant sexual problems before the operation. It was determined that 84.8% of the patients did not have any sexual problems, 9.2% had little sexual problems, and 6% had significant sexual problems after the operation. When the reasons for having sexual problems before the operation were examined, it was determined that 24.2% had feelings of losing sexual attraction, 21.2% had feelings of decreased/lost sexual desire, and 9.1% had positional difficulty. When the conditions of having sexual problems after the operation were examined, it was determined that 6.1% of them had the feeling of losing sexual attraction, and 9.1% had the feeling of a decreased/lost sexual desire. Aras et al. (32) observed that sexual problems experienced before morbid bariatric surgery decreased and body perceptions and sexual functions were positively affected 3 months after the operation. Berino et al. (33) proposed that long-term follow-up is necessary to evaluate the behavior of people who have undergone bariatric surgery to limit weight gain and damage the perception of QOL.

Panella et al. (34) proposed that pre-surgical BMI might play a role in weight regain in the long term, and this should be considered in surgical decision-making.

This study had some limitations. The small number of participants is one of them. The results obtained from the research are limited to the answers of patients who applied to a private practice in İstanbul for bariatric surgery.

CONCLUSION

The results of the study can be generalized to patients in the examination where the data were collected. Another limitation is that the data of the patients, at least for the first few years after the operation, were not evaluated.

According to the results of the study, it was observed that the surgical operation enhanced the QOL of the patients, improved their healthy lifestyle behaviors significantly, and significantly decreased the problems due to being overweight. Maintaining weight after surgery is closely related to maintaining diet, exercise, and healthy lifestyle behaviors. It can be recommended to provide training programs to patients for the protection of weight loss at certain intervals and to improve healthy lifestyle behaviors after the operation.

ETHICS

Ethics Committee Approval: Haliç University Non-invasive Clinical Research Ethics Committee approval was received (decision no: 3, date: 24.10.2018).

Informed Consent: All patients were informed about the study, and written informed consent was obtained for the protocol.

Authorship Contributions

Surgical and Medical Practices: D.A., E.Y., Concept: D.A., H.Y., Design: D.A., H.Y., Data Collection or Processing: D.A., E.Y., B.K., Analysis or Interpretation: H.Y., Literature Search: D.A., E.Y., Writing: D.A., H.Y.

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

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

REFERENCES

1. Halpern A, Mancini MC. Treatment of obesity: an update on anti-obesity medications. Obes Rev 2003;4:25-42.
2. Turkish Society of Endocrinology and Metabolism (TEMD). Obesity Diagnosis and Treatment Guide. Ankara: 2019.
3. World Health Organization. Regional Office for Europe. (2022). WHO European Regional Obesity Report 2022. World Health Organization. Regional Office for Europe. https://apps.who.int/iris/handle/10665/353747
4. Freeman RA, Overs SE, Zarshenas N, Walton KL, Jorgensen JO. Food tolerance and diet quality following adjustable gastric banding, sleeve gastrectomy and Roux-en-Y gastric bypass. Obes Res Clin Pract 2014;8:e115-200.
5. Sheka AC, Wirth KM, Ikramuddin S. Preventing Macrovascular Events With Bariatric Surgery. JAMA 2018;320:1545-7.
6. Kushner RF, Foster GD. Obesity and quality of life. Nutrition 2000;16:947-52.
7. Wimmelmann CL, Dela F, Mortensen EL. Psychological predictors of mental health and health-related quality of life after bariatric surgery: a review of the recent research. Obes Res Clin Pract 2014;8:e314-24.
8. Zheng M, Jin H, Shi N, Duan C, Wang D, Yu X, Li X. The relationship between health literacy and quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes 2018;16:201.
9. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. WHO Obesity Technical Report Series 894. Geneva, Switzerland: World Health Organization; 2000.
10. Walker SN, Sechrist KR, Pender NJ. The Health-Promoting Lifestyle Profile: development and psychometric characteristics. Nurs Res 1987;36:76-81.
11. Bahar Z, Beşer A, Gördes N, Ersin F, Kısal A. Validity and Reliability Study of Healthy Lifestyle Behavior Scale II. Journal of Cumhuriyet University School of Nursing 2008; 12: 1-12.
12. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976) 2000;25:3130-9.
13. Kocyigit H, Aydemir O, Fisek G. The validity and reliability of Turkish version of the quality of life questionnaire. Drug and Treatment Journal 1999;12:102-6.
14. Elhag W, El Ansari W. Durability of Cardiometabolic Outcomes Among Adolescents After Sleeve Gastrectomy: First Study with 9-Year Follow-up. Obes Surg 2021;31:2869-77.
15. Ustundag H, Gul A, Ozkaya B, Zengin N. Healthy Lifestyle Behaviors and Quality of Life After Sleeve Gastrectomy. Gastroenterol Nurs 2020;43:456-62.
16. Mirica RM, Ionescu M, Mirica A, Ginghina O, Iosifescu R, Rosca A, et al. Quality of life assessment after bariatric surgery—a single-center experience. Indian Journal Surgery 2017;80:435–41.
17. Yaralı S, Hacıalioğlu N, Kılınç T. Evaluation of the Healthy Lifestyle Behaviors, Eating Attitudes and Weight Status of Patients After Obesity Surgery. J Nursology 2022;25:36-44.
18. de Zwaan M, Lancaster KL, Mitchell JE, Howell LM, Monson N, Roerig JL, et al. Health-related quality of life in morbidly obese patients: effect of gastric bypass surgery. Obes Surg 2002;12:773-80.
19. Lindekilde N, Gladstone BP, Lübeck M, Nielsen J, Clausen L, Vach W, et al. The impact of bariatric surgery on quality of life: a systematic review and meta-analysis. Obes Rev 2015;16:639-51.
20. Satman I, Yilmaz T, Sengül A, Salman S, Salman F, Uygur S, et al. Population-based study of diabetes and risk characteristics in Turkey: results of the turkish diabetes epidemiology study (TURDEP). Diabetes Care 2002;25:1551-6.
21. Jumbe S, Bartlett C, Jumbe SL, Meyrick J. The effectiveness of bariatric surgery on long term psychosocial quality of life - A systematic review. Obes Res Clin Pract 2016;10:225-42
22. Pirinçci E, Acar U, Kurt O, Akkuş İ, Oğuzöncül AF, Özkan E, et al. Obesity Prevalance and Affecting Factors in 35 Years and over Population in Sivrice Education Research Area in Elazig Province. Balıkesir Medical Journal 2020;9:163-70
23. Ustu Y, Ugurlu M, Aslan O, Aksoy YM, Kasim I, Egici MT, et al. High prevalence of obesity in Tokat, a northern province of Turkey. J Pak Med Assoc 2012;62:435-40
24. Loux TJ, Haricharan RN, Clements RH, Kolotkin RL, Bledsoe SE, Haynes B, et al. Health-related quality of life before and after bariatric surgery in adolescents. J Pediatr Surg 2008;43:1275-9.
25. Chan CM, Wang WC. Quality of life in overweight and obese young Chinese children: a mixed-method study. Health Qual Life Outcomes 2013;11:33.
26. Stunkard AJ, Sørensen TI, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, et al. An adoption study of human obesity. N Engl J Med 1986;314:193-8.
27. Kiewieta RM, Duriana MF, Cuijpersb L, Hespc F, Vliet A. Quality of Life After Gastric Banding in Morbidly Obese Dutch Patients: Long-Term Follow-up. Obesity Research and Clinical Practice 2013;2:1-2.
28. Kuyucu A. Determination of Weight Loss, Dietary Intake and Some Biochemical Parameters of Patients After Bariatric Surgery Within a Follow-Up Duration of Six Months and Over. Hasan Kalyoncu University Institute of Health Sciences Nutrition and Dietetics. MSc Thesis. Gaziantep; 2018.
29. Zhang Y, Zhu C, Wen X, Wang X, Li L, Rampersad S, et al. Laparoscopic sleeve gastrectomy improves body composition and alleviates insulin resistance in obesity related acanthosis nigricans. Lipids Health Dis 2017;16:209.
30. Boissière L, Perotin-Collard JM, Bertin E, Gaubil I, Diaz Cives A, Barbe C, et al. Improvement of dyspnea after bariatric surgery is associated with increased Expiratory Reserve Volume: A prospective follow-up study of 45 patients. PLoS One 2017;12:e0185058.
31. Dixon JB, Dixon ME, O'Brien PE. Body image: appearance orientation and evaluation in the severely obese. Changes with weight loss. Obes Surg 2002;12:65-71.
32. Aras B, Uruç F, Akan S, Şahin A, Yıldırım Ç, Yüksel ÖH, et al. Effects of obesity surgery on sexual function, depression and quality of life of males. The New Journal of Urology 2017;12:38-43.
33. Berino TN, Reis AL, Carvalhal MML, Kikuchi JLD, Teixeira RCR, Gomes DL. Relationship between Eating Behavior, Quality of Life and Weight Regain in Women after Bariatric Surgery. Int J Environ Res Public Health 2022;19:7648.
34. Pañella C, Busto M, González A, Serra C, Goday A, Grande L, et al. Correlation of Gastric Volume and Weight Loss 5 Years Following Sleeve Gastrectomy. Obes Surg 2020;30:2199-205.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:104-108
DOI: 10.4274/BMJ.galenos.2023.2022.12-6

Research

Do Cytokines Play a Role in Chronic Spontaneous Urticaria in Childhood? IL-17 One of Them?

Çocukluk Çağındaki Kronik Spontan Ürtikerde Sitokinlerin Rolü Var mı? IL-17 Bunlardan Biri mi?

Deniz Özçeker[1], Esra Yücel[2], Okan Dikker[3]

[1]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Pediatric Immunology and Allergy, İstanbul, Türkiye
[2]İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Immunology and Allergy, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Biochemistry, İstanbul, Türkiye

ABSTRACT

Objective: Chronic spontaneous urticaria (CSU) is a common skin disorder that is considered to be an autoimmune disorder in a subset of patients. Because it is not always possible to find a trigger in CSU cases, it may be thought that various cytokines may play a role in the inflammatory processes associated with CSU. One of these markers is interleukin-17 (IL-17).

Methods: In this case-control study, serum IL-17 levels were measured in 50 patients with CSU and 35 healthy control subjects. Urticaria activity score (UAS-7) was used to assess disease activity.

Results: Serum levels of IL-17 in patients with CSU were not significantly different from those in healthy controls [mean and median: 3.98±3.88 (3.1) vs. 4.85±2.96 (3.9) pg/mL, p=0.063]. Serum levels of IL-17 in mild CSU patients did not differ significantly from those in moderate-severe CSU patients [mean and median: 4.24±4.33 (3.3) vs. 3.1±1.13 (3) pg/mL, p=0.30]. No significant differences in IL-17 levels were observed between autologous serum tests (ASST) (+) and ASST (-) patients with similar UAS, and serum IL-17 levels of patients did not significantly differ according to sex and antinuclear antibody positivity.

Conclusion: This is the first study to examine serum IL-17 levels in children with CSU. Further studies with a larger number of patients are needed to elucidate the role of IL-17 in the pathogenesis of childhood CSU.

Keywords: Chronic urticaria, children, interleukin -17

ÖZ

Amaç: Kronik spontan ürtiker (KSÜ), otoimmün bir bozukluk olarak da kabul edilen yaygın bir deri hastalığıdır. KSÜ olgularında her zaman tetikleyici bulmak mümkün olmadığından, KSÜ'ye bağlı enflamatuvar süreçlerde çeşitli sitokinlerin rol oynayabileceği düşünülmektedir. Bu belirteçlerden biri de interlökin-17'dir (IL-17).

Gereç ve Yöntem: Bu olgu kontrol çalışmasında, KSÜ'lü 50 hasta ve 35 sağlıklı kontrol hastasında serum IL-17 konsantrasyonu ölçüldü. Hastalık aktivitesini değerlendirmek için ürtiker aktivite skoru (UAS-7) kullanıldı.

Bulgular: KSÜ'lü hastalardaki serum IL-17 seviyeleri, sağlıklı kontrollerden önemli ölçüde farklı değildi [ortalama ve medyan: 3,98±3,88 (3,1) vs. 4,85±2,96 (3,9) pg/mL, p=0,063]. Hafif KSÜ hastalarında serum IL-17 seviyeleri, orta-şiddetli KSÜ hastalarından önemli ölçüde farklı değildi [ortalama ve medyan: 4,24±4,33 (3,3) vs. 3,1±1,13 (3) pg/mL, p=0,30]. Benzer UAS olan otolog serum testi (OST) (+) ve OST (-) hastalar arasında IL-17 düzeyleri arasında farklılıklar gözlenmedi ek olarak cinsiyet ve anti-nükleer antikor pozitifliğine göre de anlamlı farklılık izlenmedi.

Sonuç: Bu çalışma, kronik spontan ürtikerli çocuklarda serum IL-17 düzeylerini inceleyen ilk çalışmadır, IL-17'nin çocukluk çağı KSÜ patogenezindeki rolünü aydınlatmak için daha fazla sayıda hasta ile ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik ürtiker, çocuklar, interlökin-17

Address for Correspondence: Deniz Özçeker, University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Pediatric Immunology and Allergy, İstanbul, Türkiye
E-mail: denizozceker@gmail.com ORCID ID: orcid.org/0000-0002-0032-6727

Cite as: Özçeker D, Yücel E, Dikker O. Do Cytokines Play a Role in Chronic Spontaneous Urticaria in Childhood? IL-17 One of Them?. Med J Bakirkoy 2024;20:104-108

Received: 05.01.2023
Accepted: 17.10.2023

INTRODUCTION

Recurrent itchy wheals and/or angioedema lasting more than six weeks are the hallmarks of chronic spontaneous urticaria (CSU), which is caused by many known or unknown etiologies (1). Overall, the prevalence of chronic urticaria (CU) in children seems to be below 1%, and there is no significant difference among genders (2-6). Scarce data are available on the epidemiology and etiology of CU in children. The pathogenesis of CSU remains unknown possible causes include foods, drugs, infections, pseudoallergies to food and drugs, insect stings and bites, and auto reactivity related to functional autoantibodies directed against the immunoglobulin E receptor (7).

Because it is not always possible to detect a trigger in CSU cases, it may be thought that various cytokines could play a role in CSU-related inflammatory processes. One of these markers is interleukin-17 (IL-17). IL-17 is produced by T helper (Th) type 17 cells that bind to an IL-17 receptor expressed on endothelial, epithelial, and fibroblastic stromal cells. IL-17 is associated with many autoimmune disorders including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, and asthma (8-10). In this regard, IL-17 may have a role in the pathogenesis of CSU, and its levels can be a biomarker for detecting disease severity or therapeutic response in CSU. However, no study has been conducted only in children.

This study aimed to understand the role of IL-17 levels in the pathogenesis of CSU in terms of diagnosis, prognosis, and severity of the disease.

METHODS

Study Design and Participants

In this case-controlled study, fifty patients who were admitted to Okmeydanı Training and Research Hospital Pediatric Allergy Outpatient Clinic with a diagnosis of CSU and 35 age- and sex-matched healthy children were examined. A detailed history was taken from all patients, and physical was examined. Patients with urticaria vasculitis and concomitant allergic diseases and clinical evidence of physical urticaria, such as dermographism, cold urticaria, and cholinergic urticaria, were excluded. Antihistamine medications were discontinued 7 days before the study. Patients' age, sex, family history of atopy, duration of symptoms, serum total IgE levels, eosinophil percentage in complete blood count, antinuclear antibody, and results were recorded from patient files.

All patients' anti-histaminic treatments were discontinued for 10 days before IL-17 serum samples were collected.

Data Collection

Serum IL-17 Analysis

2 mL of blood were taken from the volunteers for IL-17 serum testing. The serum was held at room temperature for 20 min, centrifuged at 4000 rpm for 10 min, and stored at a temperature of -80 °C. We left the serums to dissolve at room temperature on the day of the analysis. Ready-to-use immune enzymatic test (ELISA) kits were used to detect IL-17A levels in the serum samples of participants. Serum IL-17 levels were analyzed using a kit branded Robonic ELISA plate reader®, ELISA, India. The results of analytical measurements were between 1.6 and 100 pg/mL for IL-17A. The minimal detection limit was 0.5 pg/mL.

The detected intra- and inter-assay variation coefficients were 7.1 % and 9.1 %, respectively.

Assessing Urticaria Severity

The disease activity and urticaria severity were assessed with the urticaria activity score 7 (UAS-7), which was calculated indirectly according to the recommendations of the EAACI/GA2LEN/EDF/WAO Guidelines (11). Patients were asked to record their assessment scores for 7 days using the UAS-7 and were grouped as mild, moderate, and severe.

Autologous Serum Tests

First, 10 mL of venous blood was taken from the patients into sterile plain tubes and left to coagulate for 30 min at room temperature. Blood was then centrifuged for 15 min at 500 g, and serum was eluted. ASST was conducted using 0.5 mL of the patient's own serum, and the physiological serum was injected intradermally into the flexor aspect of the forearm.

The greater than 1.5 mm or the diameter of the saline papule was accepted as a positive result after waiting for 30 min.

All ASSTs were performed by the same researcher.

Statistical Analysis

To evaluate the results of the study, IBM SPSS Statistics 22 was used for statistical analysis programs (SPSS IBM, Türkiye).

When assessing the operating data, the conformity of the parameters to the normal distribution was evaluated using the Shapiro-Wilks test. Continuous variables that were not normally distributed were presented as intermediates with interquartile intervals and were statistically analyzed using the Mann-Whitney U test. The chi-square test was used to determine categorical variables, presented in counts or percentages. Statistical significance was evaluated at $p<0.05$.

Ethics

This study was approved by the Okmeydanı Training and Research Hospital Clinical Research Ethics Committee (decision no: 1001, date: 09.10.2018). All subjects provided written informed consent before participation.

RESULTS

Demographic Data and Patient Characteristics

A total of 85 children (50 patients, 35 controls) were evaluated in this study. The median age was 10 (quartiles: 7.5-14) years, and 50.6% (n=43) were male. The median duration of symptoms was 3.5 (minimum-maximum: 2-40) months. There was no difference in age or sex between the patient and control groups.

The majority of our patients had mild to moderate disease severity, and other clinical findings are presented in Table 1.

Cytokine Data

Serum levels of IL-17 in patients with CSU were not significantly different from healthy controls [median (quartiles): 3.1 (2.6-4.6) vs. 3.9 (3.0-6.3) pg/mL, p=0.063; Figure 1] (Table 2).

Levels of IL-17 in mild CSU patients did not differ significantly versus moderate-severe CSU patients [median (quartiles): 3.3 (2.6-4.9) vs. 3.0 (2.5-3.7) pg/mL, p=0.30].

Table 1. Demographic and clinical characteristics of patients with CSU

	n	%
Sex female/male	24/26	48/52
Angioedema (n=50)$_{n,\%}$	13	26
Family history of atopy (n=50)$_{n,\%}$	6	12
Additional-allergic diseases		
No	41	82
Yes*	9	18
UAS (n=50)$_{n,\%}$		
Mild	39	78
Moderate	10	20
Severe	1	2
ASST (n=30)$_{n,\%}$ positivity	13	43
ANA (n=50)$_{n,\%}$ positivity	11	22
Skin prick test positivity (n=38)$_{n,\%}$	12	31.6
	Median	**Min-max**
Total IgE levels (Ku/L)	63.1	2.8-811
Eosinophil levels (%)	2	0.1-11.2

CSU: Chronic spontaneous urticaria, ASST: Autologous serum test, ANA: Antinuclear antibody, IgE: Immunoglobulin E, UAS: Urticaria activity score, min-max: Minimum-maximum
*Asthma (n=6), allergic rhinitis (n=2), atopic dermatitis (n=1)

No significant differences in IL-17 levels were observed between ASST (+) and ASST (-) patients with similar UAS, and serum IL-17 levels of patients did not significantly differ according to sex and antinuclear antibody positivity (Table 2).

DISCUSSION

CSU pathogenesis has not been fully understood. In this study, although CSU patients had lower serum IL-17 levels than healthy subjects, the difference was not statistically significant. There are many studies about IL-17 and CU, but the results are very controversial, and there are no studies conducted in children (12-18).

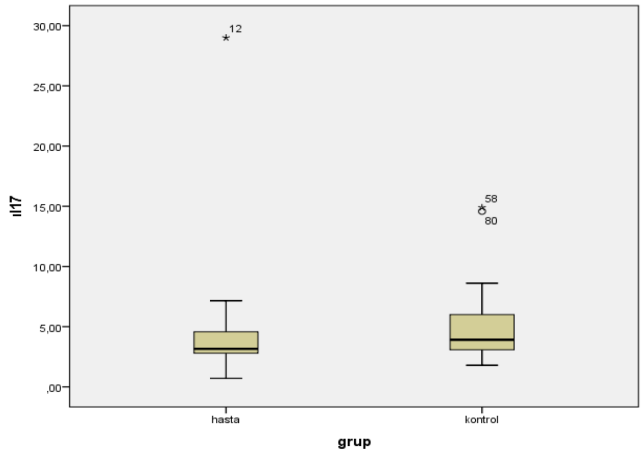

Figure 1. Comparison of plasma levels of IL-17 between CSU patients and control groups
IL-17: Interleukin 17, CSU: Chronic spontaneous urticaria

Table 2. Evaluation of IL-17 levels in patients with CSU according to groups, gender, ASST, ANA positivity, and severity of the disease by UAS

		IL-17 level Median (min-max)	p-value
Group	Patient group	3.1 (2.6-4.6)	0.63
	Control group	3.9 (3.0-6.3)	
Sex	Female	4.1 (2.9-5.6)	0.015*
	Male	3.3 (2.4-3.9)	
ASST	Negative	3.0 (2.0-4.1)	0.572
	Positive	3.1 (2.0-5.1)	
ANA	Negative	3.1 (2.8-4.5)	0.879
	Positive	3.0 (1.9-4.9)	
UAS	Mild	3.3 (2.6-4.9)	0.303
	Moderate	3.0 (2.5-3.7)	

Mann-Whitney U test, *p<0.05. PS: One of the children with a severe UAS score was excluded from the analysis.
CSU: Chronic spontaneous urticaria, ASST: Autologous serum test, ANA: Antinuclear antibody, IL-17: Interleukin 17, UAS: Urticaria activity score, min-max: Minimum-maximum

Daschner et al. (12) reported lower IL-17 serum levels in only adults with CSU. They found lower serum IL-17 levels in patients with CSU with or without sensitization against Anisakis simplex. Th17 cell functions may be insufficient and IL-17 levels may be suppressed in patients with CSU (12). Degirmenci et al. (13) reported no significant difference in serum IL-17 levels between CSU patients and healthy controls. In contrast, Atwa et al. (14) reported increased IL-17 serum levels in CSU patients older than 12 years, which was related to disease severity. Dos Santos et al. (15) found that the IL-17 level of CU patients is higher than that of control patients. Chen et al. (16) found higher serum levels of IL-17 in adults, especially in ASST-positive patients. Similarly, Lin et al. (17) detected higher serum IL-17 concentrations in adult patients with CSU. We believe that these variable outcomes may have resulted from the different types of urticaria, as indicated by Daschner et al. (12).

Th17 cells and their cytokine, IL-17, result in the secretion of several inflammatory factors and autoantibody production; thus, they serve an important role in the initiation and maintenance of autoimmune and inflammatory processes in variable disorders (19). Serum IL-17 plays a role in other allergic diseases; therefore, diverse results can be obtained in various allergic diseases. If we had included those with concomitant allergic disease, we might have found lower serum levels of IL-17 in patients with CSU. A potential role of IL-17 has been described in the pathology of inflammatory skin disorders, such as atopic dermatitis, contact hypersensitivity, and psoriasis. This indicates that IL-17 is an important mediator of tissue inflammation; however, high intense expression of IL-17A was shown in the skin of patients with CSU, both in lesional or non-lesional skin biopsies, compared with healthy skin (20). In this study, there was no difference in serum IL-17 levels among ASST (-) and ASST (+) CSU patients. Previous studies demonstrated that serum levels of tumour necrosis factor-α, IL-10, IL-13, IL-17, and IL-23 were higher in ASST (+) than in ASST (-) CSU patients (14-16, 20).

Degirmenci et al. (13) reported no significant difference in serum IL-17 levels according to ASST results. In line with our results, the ASST (-) patient group had significantly lower IL-17 levels than the control group. Serum levels of IL-17 did not differ in ASST (-) and ASST (+) patients in the study by Grzanka et al. (18), similar to the results of our study.

CSU patients with mild, moderate, or severe symptoms and healthy subjects had no differences in serum IL-17 levels. Similarly, Grzanka et al. (18) did not find a relationship between serum IL-17 levels and disease severity determined using UAS-7. Atwa et al. (14) showed a significant correlation between disease activity as assessed by UAS-7 for 7 days before blood sampling and serum IL-17 concentration. They specified that elevated IL-17 resulted from the activation of mast cells involved in urticarial processes. The most numerous cells containing IL-17 in human skin are mast cells, lymphocytes, and neutrophils. Diverse stimuli result in these cells producing IL-17. It may be speculated that IL-17-producing Th17 cells and IL-17 levels vary according to urticaria severity. In our study, we did not notice any relationship between UAS-7 and serum IL-17 levels, which may be attributed to the low number of patients in the severe group.

CONCLUSION

In conclusion, IL-17 may not have an important role in childhood CSU pathogenesis because no significant difference was found in serum IL-17 levels between CSU patients and healthy children, and no correlation was found with disease severity. This is the first study to examine serum IL-17 levels in children with chronic spontaneous urticaria. Further studies with a larger number of patients are needed to elucidate the role of IL-17 in the pathogenesis of childhood CSU.

ETHICS

Ethics Committee Approval: This study was approved by the Okmeydanı Training and Research Hospital Clinical Research Ethics Committee (decision no: 1001, date: 09.10.2018).

Informed Consent: All subjects provided written informed consent before participation.

Authorship Contributions

Surgical and Medical Practices: D.Ö., E.Y., O.D., Concept: D.Ö., E.Y., Design: D.Ö., E.Y., Data Collection or Processing: D.Ö., E.Y., Analysis or Interpretation: D.Ö., E.Y., O.D., Literature Search: D.Ö., E.Y., Writing: D.Ö.

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

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

REFERENCES

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018;73:1393-414.
2. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. Clin Exp Dermatol 2010;35:869-73.
3. Lee SJ, Ha EK, Jee HM, Lee KS, Lee SW, Kim MA, et al. Prevalence and Risk Factors of Urticaria With a Focus on Chronic Urticaria in Children. Allergy Asthma Immunol Res 2017;9:212-9.

4. Cantarutti A, Donà D, Visentin F, Borgia E, Scamarcia A, Cantarutti L, et al. Epidemiology of Frequently Occurring Skin Diseases in Italian Children from 2006 to 2012: A Retrospective, Population-Based Study. Pediatr Dermatol 2015;32:668-78.
5. Broder MS, Raimundo K, Antonova E, Chang E. Resource use and costs in an insured population of patients with chronic idiopathic/spontaneous urticaria. Am J Clin Dermatol 2015;16:313-21.
6. Brüske I, Standl M, Weidinger S, Klümper C, Hoffmann B, Schaaf B, et al. Epidemiology of urticaria in infants and young children in Germany--results from the German LISAplus and GINIplus Birth Cohort Studies. Pediatr Allergy Immunol 2014;25:36-42
7. Greaves MW. Chronic idiopathic urticaria. Curr Opin Allergy Clin Immunol 2003;3:363-8.
8. Grattan CE, Wallington TB, Warin RP, Kennedy CT, Bradfield JW. A serological mediator in chronic idiopathic urticaria--a clinical, immunological and histological evaluation. Br J Dermatol 1986;114:583-90.
9. Ziolkowska M, Koc A, Luszczykiewicz G, Ksiezopolska-Pietrzak K, Klimczak E, Chwalinska-Sadowska H, et al. High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via cyclosporin A-sensitive mechanism. J Immunol 2000;164:2832-8.
10. Liu ZJ, Yadav PK, Su JL, Wang JS, Fei K. Potential role of Th17 cells in the pathogenesis of inflammatory bowel disease. World J Gastroenterol 2009;15:5784-8.
11. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. Methods report on the development of the 2013 revision and update of the EAACI/GA2 LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2014;69:e1-29.
12. Daschner A, Rodero M, DE Frutos C, Valls A, Vega F, Blanco C, et al. Different serum cytokine levels in chronic vs. acute Anisakis simplex sensitization-associated urticaria. Parasite Immunol 2011;33:357-62.
13. Degirmenci PB, Kırmaz C, Vatansever S, Onur E, Nal E, Erdin S, et al. Analysis of the association of chronic spontaneous urticaria with interlekin-4, -10, transforming growth factor-β1, interferon-γ, interleukin-17A and -23 by autologous serum skin test. Postepy Dermatol Alergol 2017;34:70-6.
14. Atwa MA, Emara AS, Youssef N, Bayoumy NM. Serum concentration of IL-17, IL-23 and TNF-α among patients with chronic spontaneous urticaria: association with disease activity and autologous serum skin test. J Eur Acad Dermatol Venereol 2014;28:469-74.
15. Dos Santos JC, Azor MH, Nojima VY, Lourenço FD, Prearo E, Maruta CW, et al. Increased circulating pro-inflammatory cytokines and imbalanced regulatory T-cell cytokines production in chronic idiopathic urticaria. Int Immunopharmacol 2008;8:1433-40.
16. Chen Q, Zhong H, Chen WC, Zhai Z, Zhou Z, Song Z, et al. Different expression patterns of plasma Th1-, Th2-, Th17- and Th22-related cytokines correlate with serum autoreactivity and allergen sensitivity in chronic spontaneous urticaria. J Eur Acad Dermatol Venereol 2018;32:441-8.
17. Lin W, Zhou Q, Liu C, Ying M, Xu S. Increased plasma IL-17, IL-31, and IL-33 levels in chronic spontaneous urticaria. Sci Rep 2017;7:17797.
18. Grzanka A, Damasiewicz-Bodzek A, Kasperska-Zajac A. The relationship between circulating concentrations of interleukin 17 and C reactive protein in chronic spontaneous urticaria. Allergy Asthma Clin Immunol 2017;13:25.
19. Hueber AJ, Asquith DL, Miller AM, Reilly J, Kerr S, Leipe J, et al. Mast cells express IL-17A in rheumatoid arthritis synovium. J Immunol 2010;184:3336-40.
20. Toubi E, Vadasz Z. The Emerging Role of IL-17 in the Immune-Pathogenesis of Chronic Spontaneous Urticaria. Immunotargets Ther 2020;9:217-23.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:109-114
DOI: 10.4274/BMJ.galenos.2023.2023.5-8

Research

Hemiarthroplasty or Internal Fixation in Intertrochanteric Fractures? Let's Ask the Caregivers

İntertrokanterik Kırıklarda Hemiartroplasti mi Yoksa İnternal Tespit mi? Bakıcılara Soralım

Gökhan Peker, Onur Varış

University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital, Clinic of Orthopaedics and Traumatology, Trabzon, Türkiye

ABSTRACT

Objective: Intertrochanteric femur fractures (ITFs) in the elderly are most often treated with internal fixation or hemiarthroplasty. The contribution of caregivers in the recovery process of these patients is also important. Previous studies have generally examined these two treatment options on the basis of their functional results in patients. This study aimed to compare the two procedures in terms of their effects on patients' caregivers.

Methods: This prospective study included caregivers of patients with ITFs between May 2021 and April 2022. Caregivers were categorized into two groups according to the received treatment: those who underwent hemiarthroplasty and those who received internal fixation. The Zarit Caregiving Burden Interview (ZBI) was used to evaluate and compare the burden score of the caregivers between groups at the beginning and end of the study.

Results: Caregivers of 120 patients who underwent hemiarthroplasty (60) and internal fixation (60) were included in the study. The time to the first mobilization of the hemiarthroplasty group was significantly shorter than that of the internal fixation ($p<0.001$). Caregivers in both groups had a significant increase in ZBI values at 6-month follow-up visits ($p<0.01$) There was no statistically significant difference between the pre-operative and postoperative 6th month scores and the amount of increase between groups ($p=0.178$, 0.629, 0.372, respectively).

Conclusion: Compared with the pre-operative period, caregiver burden increased significantly in both groups, but there was no significant difference between the changes in caregiver burden. The type of surgery performed has no impact on caregiver burden.

Keywords: Hemiarthroplasty, internal fixation, caregiver, Zarit Burden Interview

ÖZ

Amaç: Yaşlılarda intertrokanterik femur (İTF) kırıkları çoğunlukla internal fiksasyon veya hemiartroplasti ile tedavi edilir. Bu hastaların iyileşme sürecinde bakım verenlerin katkısı da önemlidir. Önceki çalışmalarda genellikle bu iki tedavi seçeneği hastalardaki fonksiyonel sonuçlara göre incelenmiştir. Bu çalışma, iki prosedürü hastaların bakım verenleri üzerindeki etkileri açısından karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu prospektif çalışma, Mayıs 2021 ile Nisan 2022 arasında İTF kırığı olan hastaların bakım verenlerini içermektedir. Bakım verenler uygulanan tedaviye göre hemiartroplasti ve internal fiksasyon yapılanlar olarak iki gruba ayrıldı. Bakım verenlerin çalışmanın başında ve sonunda gruplar arasında yük puanlarını değerlendirmek ve karşılaştırmak için Zarit Bakım Verici Yükü (ZBVY) ölçeği kullanılmıştır.

Bulgular: Çalışmaya hemiartroplasti (60) ve internal tespit (60) uygulanan 120 hastanın bakım verenleri dahil edildi. Hemiartroplasti grubunda ilk mobilizasyona kadar geçen süre internal fiksasyon uygulanan gruba göre anlamlı olarak daha kısaydı ($p<0,001$). Her iki grupta da bakım verenlerin 6. ay kontrollerinde ZBVY değerlerinde anlamlı artış saptandı ($p<0,01$) Ameliyat öncesi ve sonrası 6. ay puanları ve gruplar arası artış miktarı arasında istatistiksel olarak anlamlı fark yoktu ($p=0,178$, sırasıyla 0,629, 0,372).

Sonuç: Ameliyat öncesi döneme göre her iki grupta da bakım veren yükü anlamlı olarak arttı ancak bakım veren yükündeki değişimler arasında anlamlı bir fark yoktu. Yapılan ameliyatın çeşidinin bakıcı yükü üzerinde etkisi yoktur.

Anahtar Kelimeler: Hemiartroplasti, internal fiksasyon, bakıcı, Zarit Yük görüşmesi

Address for Correspondence: Gökhan Peker, University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital, Clinic of Orthopaedics and Traumatology, Trabzon, Türkiye
Phone: 532 588 70 51 E-mail: drgokhanpeker@gmail.com ORCID ID: orcid.org/0000-0002-6211-6645

Cite as: Peker G, Varış O. Hemiarthroplasty or Internal Fixation in Intertrochanteric Fractures? Let's Ask the Caregivers. Med J Bakirkoy 2024;20:109-114

Received: 22.05.2023
Accepted: 17.10.2023

INTRODUCTION

Intertrochanteric femur fractures (ITFs) are common injuries that cause significant morbidity and mortality in elderly (1). The incidence has increased worldwide as life expectancy increases. Although epidemiologic data vary between countries, it is estimated that hip fractures currently affect approximately 18% of females and 6% of males globally (2). ITFs in the elderly cause physical dysfunction with the loss of independent mobility and place a significant burden on patients and caregivers.

Modern treatment methods aim for rapid mobilization and low complication rates. According to recent reports, there is diversity among orthopedic surgeons concerning the optimal treatment of ITF fractures and the changing trends in management (3). Most patients are treated surgically unless they have comorbidities that preclude surgery or a low life expectancy (4). Surgical procedures for treatment also increase in parallel with the incidence of fractures (5). They can be roughly divided into arthroplasty and internal fixation methods that preserve the hip bone stock; however, there were no significant differences in functional outcome (6). The method to be used depends on the location and type of fracture and surgeon's preference. Proximal femoral nailing (PFN) is the most common internal fixation method. The success of PFN in early weight bearing is lower than that of hemiarthroplasty (1). The postoperative inability to bear weight and therefore immobilization reduces the quality of life of patients in the early postoperative period.

The clinical outcomes and quality of life of the patients during the postoperative period also affect the care processes and the quality of life of caregivers. Many studies have been conducted on the effects of surgical methods on clinical outcomes, but the number of studies examining the effects of these methods on the caregivers of patients is limited. Pre-identifying caregivers who are probably overburdened by patient care and evaluating and preventing problems related to stressful caregiving situations throughout the care process will be helpful in enhancing the quality of caregiving and avoiding the need for a long-term care facility for hip fracture patients (7).

This study aimed to evaluate and compare the effects of internal fixation and hemiarthroplasty on the quality of life of caregivers for treating ITFs in the elderly.

METHODS

This prospective study included caregivers of patients admitted to the emergency department of our hospital with a diagnosis of ITF and operated between May 2021 and April 2022. All participants' consent was obtained. Our study was submitted to the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital and started after approval was obtained (decision no: 2021/74, date: 02.05.2021). To evaluate the burden score of the primary caregiver at the beginning and end of the study period and its association with the surgical intervention method, a prospective cohort study was conducted using a questionnaire. A total of 120 patient caregivers were enrolled in the study.

Internal fixation or hemiarthroplasty was performed in patients who underwent surgery for hip fracture. PFN was used as the internal fixation method. Postoperatively, patients and participants were followed up for at least 6 months.

Inclusion criteria were as follows: the patient had a family member or a non-family member who was responsible for the patient's care, the patient was not in need of care in the pre-operative period and could mobilize on his/her own, the patient was followed up for at least 6 months post-discharge, while bone union was completed, and the patient was over 60 years of age. Exclusion criteria were the presence of peripheral arterial disease, dementia, neurologic diseases such as Parkinson's disease and rheumatologic diseases, postoperative complications such as delayed union, nonunion, infection, embolism, and termination of follow-up before the 6th month.

In 1985, Zarit et al. (8) developed the Zarit Burden Interview (ZBI) to subjectively assess the level of caregiving burden in chronic diseases. A validity study of the scale in Türkiye was conducted by İnci in 2006. The scale comprises 22 questions and has a Likert-type rating ranging from 0 to 4 on a scale of never, rarely, sometimes, frequently, often, or almost always (9). The evaluation of the ZBI, in which all items are expressed in plain language, is based on the total score. The higher the score, the higher the care burden, and the maximum score is 88. 0-21 is interpreted as little or no burden, 21-40 as mild to moderate burden, 41-60 as moderate to severe burden, and 61-88 as severe burden.

Data Collection

The ZBI form was completed immediately before and six months after surgery. Patients were divided into two groups: those who underwent internal fixation and those who underwent hemiarthroplasty. The age, gender, educational level of the caregiver, duration of care (years), number of hours spent together per day, presence of any diagnosed physical or psychological illness, age, gender, educational level, and immobilization time until the first partial weight bearing after surgery of the care recipient were recorded

using a sociodemographic data form. The groups were compared before and six months after surgery, and comparisons between groups were also made.

Statistical Analysis

This article's statistical analyses were performed using WisdomEra's statistical tool, Wanalyzer v1.4.53, a data analytics platform using the SciPy v1.2.3 library. SciPy (pronounced "Sigh Pie") is a Python-based ecosystem of open-source software for mathematics, science, and engineering. Using descriptive analysis, the mean, minimum-maximum (min-max), and standard deviation values of the data were obtained. The difference between the two independent groups was examined by applying the t-sample test for normally distributed data. When there was a group that did not show a normal distribution between the groups, the Kruskal-Wallis method was used to test the significance of the difference between the means of three or more groups. This method is the non-parametric equivalent of one-way ANOVA. The normal distribution of the data was evaluated under the condition that the p-value was higher than 0.05. At the same time, a normal distribution range of the data was observed for -1.5/+1.5.

RESULTS

In total, caregivers of 120 patients who underwent 60 (50%) hemiarthroplasty and 60 (50%) internal fixation were included in the study.

Caregiver Characteristics

Of the 120 caregivers [mean age, 49.2 (min: 20, max: 76)], 73 (61%) were female and 47 (39%) were male. Of the caregivers, 47% were adult children of the patients (21% boys, 26% girls), 7% were spouses, and 46% were others. The mean time spent by caregivers for patients was 4.82 months (Table 1).

Patient Characteristics

Of the 120 patients [mean age, 77.45 years (min: 55, max: 97)] included in the analysis, 61.7% were females and 38.3% were males. In the hemiarthroplasty group, the mean age of the 60 patients (34 females and 26 males) was 78.65 years. In the internal fixation group, the mean

Table 1. Demographic data of patients and caregivers

	Patients with hemiarthroplasty	Patients with internal fixation	Total patients
	n (%)	n (%)	n (%)
Patients	60 (50%)	60 (50%)	120 (100%)
Sex			
Male	26 (43%)	20 (33%)	46 (38%)
Female	34 (57%)	40 (67%)	74 (62%)
Age (years)	78.6	76.2	77.4
Time to first mobilization after fracture (days)	2.2 (1-5)	6.5 (3-12)	4.4
Caregivers, sex			
Male	24 (40%)	23 (38%)	47 (39%)
Female	36 (60%)	37 (62%)	73 (61%)
Age (years)	50.1	48.4	49.3
Education level			
Primary school	15 (25%)	12 (20%)	27 (22%)
Secondary school	11 (18%)	10 (17%)	21 (18%)
High school	22 (37%)	28 (47%)	50 (42%)
University	6 (10%)	6 (10%)	12 (10%)
Illiterate	6 (10%)	4 (6%)	10 (8%)
Duration of care (months)	4.73	4.9	4.8
Duration of daily maintenance time (hours)	21.4	20.6	21
Relationship			
Spouse	3 (5%)	5 (9%)	8 (7%)
Son	11 (19%)	14 (23%)	25 (21%)
Daughter	14 (23%)	17 (28%)	31 (26%)
Other	32 (53%)	24 (40%)	56 (46%)

age of the 60 patients (40 men and 20 women) was 76.25 years. No significant difference was found between the groups in terms of patient age (p=0.078). A statistically significant difference was found between the groups in terms of immobilization times until the first partial weight bearing after surgery (p<0.001). The mean immobilization time until the first partial weight bearing after surgery was 2.2 days in the hemiarthroplasty group and 6.5 days in the internal fixation group (Table 1).

Caregiver Burden

In the hemiarthroplasty group, the mean preoperative ZBI value was 25.25 (range, 19-40) and 24.22 (range, 19-40) in the internal fixation group; both groups were not significantly different (p=0.178). The mean ZBI values at 6 months postoperatively were 41.15 (range, 26-58) and 42.25 (range, 10-85) in the hemiarthroplasty and internal fixation groups, respectively. Both groups were not significantly different (p= 0.629) (Table 2).

Caregivers in both groups had a significant increase in ZBI values at the 6-month follow-up visits (p<0.01) (Table 2). The Kruskal-Wallis test was used to test whether there was a statistical difference between the Zarit score increase percentage variables in the hemiarthroplasty and internal fixation groups (p-value: 0.374). No statistically significant difference was found between the groups.

DISCUSSION

The second most common cause of hospital admission in the elderly population is hip fractures (10). Treatment methods for hip fractures vary according to the location of the fracture, age of the patient, and surgeon's preference. Providing care for people with hip fractures is complicated and difficult because patients are often elderly and have comorbidities. The burden assumed by caregivers of patients with hip fracture can negatively affect the caregiver's quality of life, relationships, and decision to care for the patient (7). In this study, we investigated and compared the burden of caregivers in the pre-operative and postoperative periods according to surgical methods in patients who underwent hip hemiarthroplasty and internal fixation surgery after hip fracture. There was no significant difference between the changes in caregiver burden. The type of surgery performed has no impact on caregiver burden.

One month post-operative mortality rate after hip fracture surgery is approximately 10%. In patients surviving for up to 30 days, there is a significant disability risk, which can result in loss of independent mobility. Loss of independence has previously been shown to increase caregiver burden by causing difficulty in activities of daily living (11). A significant group of caregivers of elderly patients with hip fractures experience relational, physical, and mental health problems resulting from intensive caregiving in the first six months (12). There have been many studies comparing internal fixation and hemiarthroplasty as surgical treatment methods for hip fractures in different aspects, but there are no studies on the impact of these methods on the burden of caregivers.

While non-surgical conservative treatment methods are generally preferred in non-displaced fractures and in patients with comorbidities that prevent surgery, hip fractures are mostly treated with surgical methods. Internal fixation is the treatment of choice for patients with non-displaced femoral neck fractures (Garden type I or II). Arthroplasty is generally preferred to internal fixation for treating displaced femoral neck fractures in patients aged 65 years and older. Functional outcome and quality of life were achieved within 1 year after total hip arthroplasty and hemiarthroplasty and were found to be better than internal fixation (13,14). Because the blood supply to the femoral head is usually intact, intertrochanteric hip fractures are primarily stabilized by internal fixation with a sliding hip screw or intramedullary nail (15). Some surgeons also perform hemiarthroplasty for the treatment of intertrochanteric fractures.

The type of surgery performed affects the time required to return to activities of daily living and therefore the quality of life. There are studies showing that patients with fractured femoral neck treated with hip prostheses are superior to those treated with osteosynthesis in terms of quality of life (16,17). Moerman et al. (17) found that patients with hip fractures treated with osteosynthesis had a greater loss in health-related quality of life (HRQoL) in the first three

Table 2. Zarit score change value

	Preoperative Zarit score		6th month Zarit score		Zarit score increase amount			Zarit score increase rates (%)			Total
	Mean	Min-max	Mean	Min-max	Mean	Min-max	p-value	Mean	Min-max	p-value	
Hemiarthroplasty	25.2	19.0-40.0	41.1	26.0-58.0	15.9	2.0-29.0	<0.001	63.9	5.0-126.0	<0.001	60
Internal fixation	24.2	19.0-40.0	42.2	19.0-85.0	18.0	0.0-46.0	<0.001	70.3	0.0-166.0	<0.001	60
Total	24.7	19.0-40.0	41.7	19.0-85.0	16.9	0.0-46.0	<0.001	67.1	0.0-166.0	<0.001	120

Min-max: Minimum-maximum

months compared with those treated with arthroplasty, whereas those who underwent osteosynthesis had a greater improvement in HRQoL between 3 months and 1 year. They found an equal loss of HRQoL between osteosynthesis and prosthesis in the first year (17). Kim et al. (18) investigated reoperation rates, mortality, and changes in walking ability in patients who underwent bipolar hemiarthroplasty and internal fixation after intertrochanteric fracture and showed that hemiarthroplasty was associated with a lower reoperation rate and a lower rate of decreased walking ability compared with internal fixation. Because postoperative loading after arthroplasty may be faster than internal fixation in femoral neck fractures, there are studies supporting the preference of arthroplasty over internal fixation, particularly in people aged 65 years and older (15). It is an advantage for patients to get up and walk early and return to their daily life activities early. In this study, the immobilization time from surgery to the time of the first partial weight bearing was found to be shorter in the hemiarthroplasty group.

In their study, Parry et al. (7) evaluated the caregivers of 29 patients treated for hip fracture with a total follow-up of 6 months. Depressive mood was associated with high caregiver burden. The authors found that 20% of hip fracture caregivers experienced a high degree of burden and had a higher likelihood of considering placing the patient in a long-term care facility. They stated that risk factors for high caregiver burden need to be identified to prevent this (7). Nahm et al. (19) reported that despite hospital costs and all its challenges, caregiving is a positive opportunity for caregivers to spend more time with their loved ones. In contrast, overburdened caregivers have a negative impact on patient recovery (20). Therefore, it can be concluded that caregiver burden is also related to the treatment provided. Considering caregivers of hip fracture patients as part of the treatment during the patient's recovery process and providing education on patient care, transportation, and walking support of patients during their time in hospital can be helpful to reduce caregiver burden. Considering the effect of the surgical method applied on the early walking of the patients, it can be considered that there may be a relationship between the surgical treatment method and the quality of life of the caregivers. Caregivers of elderly patients, those with low pre-fracture functional status, and those with postoperative complications should receive more attention before hospital discharge and more help at home to reduce caregiver burden (21).

The present study had some limitations: the sex, educational level, and relationship with the patients in the caregiver groups were not homogeneous. Patients treated with PFN as an internal fixation method were included in the study, whereas those treated with compression plate and screws, cannulated screws, and dynamic hip screws were not. Another limitation was the short follow-up period of 6 months.

CONCLUSION

In our study, we examined the change in the burden of caregivers of patients with hip fracture treated with two different surgical methods. Patients' postoperative decreased ability to load and walk negatively affects their independent mobility and increases the burden on caregivers to meet their needs. Compared with the pre-operative period, caregiver burden increased significantly in both groups, but there was no significant difference between the changes in caregiver burden. The type of surgery performed has no impact on caregiver burden.

ETHICS

Ethics Committee Approval: Our study was submitted to the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital and started after approval was obtained (decision no: 2021/74, date: 02.05.2021).

Informed Consent: All participants' consent was obtained.

Authorship Contributions

Concept: G.P., Design: G.P., Data Collection or Processing: G.P., O.V., Analysis or Interpretation: G.P., O.V., Literature Search: G.P., O.V., Writing: G.P., O.V.

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

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

REFERENCES

1. Song QC, Dang SJ, Zhao Y, Wei L, Duan DP, Wei WB. Comparison of clinical outcomes with proximal femoral nail anti-rotation versus bipolar hemiarthroplasty for the treatment of elderly unstable comminuted intertrochanteric fractures. BMC Musculoskelet Disord 2022;23:628.
2. Veronese N, Kolk H, Maggi S. Epidemiology of Fragility Fractures and Social Impact. 2020 Aug 21. In: Falaschi P, Marsh D, editors. Orthogeriatrics: The Management of Older Patients with Fragility Fractures. 2nd ed. Cham (CH): Springer; 2021.
3. Florschutz AV, Langford JR, Haidukewych GJ, Koval KJ. Femoral neck fractures: current management. J Orthop Trauma 2015;29:121-9.
4. LeBlanc KE, Muncie HL Jr, LeBlanc LL. Hip fracture: diagnosis, treatment, and secondary prevention. Am Fam Physician 2014;89:945-51.
5. Collin PG, D'Antoni AV, Loukas M, Oskouian RJ, Tubbs RS. Hip fractures in the elderly-: A Clinical Anatomy Review. Clin Anat 2017;30:89-97.

6. Tang P, Hu F, Shen J, Zhang L, Zhang L. Proximal femoral nail antirotation versus hemiarthroplasty: a study for the treatment of intertrochanteric fractures. Injury 2012;43:876-81.
7. Parry JA, Langford JR, Koval KJ. Caregivers of hip fracture patients: The forgotten victims? Injury 2019;50:2259-62.
8. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist 1980;20:649-55.
9. Zarit SH, Zarit JM. The Memory and Behavior Problems Checklist and the Burden Interview. University Park, PA: Pennsylvania State University Gerontology Center; 1990.
10. Karaman Ö, Özkazanlı G, Orak MM, Mutlu S, Mutlu H, Çalışkan G, et al. Factors affecting postoperative mortality in patients older than 65 years undergoing surgery for hip fracture. Ulus Travma Acil Cerrahi Derg 2015;21:44-50.
11. Diameta E, Adandom I, Jumbo SU, Nwankwo HC, Obi PC, Kalu ME. The Burden Experience of Formal and Informal Caregivers of Older Adults With Hip Fracture in Nigeria. SAGE Open Nurs 2018;4:2377960818785155.
12. van de Ree CLP, Ploegsma K, Kanters TA, Roukema JA, De Jongh MAC, Gosens T. Care-related Quality of Life of informal caregivers of the elderly after a hip fracture. J Patient Rep Outcomes 2017;2:23.
13. Bhandari M, Devereaux PJ, Swiontkowski MF, Tornetta P 3rd, Obremskey W, Koval KJ, et al. Internal fixation compared with arthroplasty for displaced fractures of the femoral neck. A meta-analysis. J Bone Joint Surg Am 2003;85:1673-81.
14. Keating JF, Grant A, Masson M, Scott NW, Forbes JF. Randomized comparison of reduction and fixation, bipolar hemiarthroplasty, and total hip arthroplasty. Treatment of displaced intracapsular hip fractures in healthy older patients. J Bone Joint Surg Am 2006;88:249-60.
15. Bhandari M, Swiontkowski M. Management of Acute Hip Fracture. N Engl J Med 2017;377:2053-62.
16. Valavičienė R, Smailys A, Macijauskienė J, Hommel A. Factors affecting health-related quality of life in patients after femoral neck fracture. Medicina (Kaunas) 2010;46:801-5.
17. Moerman S, Vochteloo AJ, Tuinebreijer WE, Maier AB, Mathijssen NM, Nelissen RG. Factors associated with the course of health-related quality of life after a hip fracture. Arch Orthop Trauma Surg 2016;136:935-43.
18. Kim JW, Shon HC, Song SH, Lee YK, Koo KH, Ha YC. Reoperation rate, mortality and ambulatory ability after internal fixation versus hemiarthroplasty for unstable intertrochanteric fractures in elderly patients: a study on Korean Hip Fracture Registry. Arch Orthop Trauma Surg 2020;140:1611-8.
19. Nahm ES, Resnick B, Orwig D, Magaziner J, Degrezia M. Exploration of informal caregiving following hip fracture. Geriatr Nurs 2010;31:254-62.
20. Shyu YI, Chen MC, Wu CC, Cheng HS. Family caregivers' needs predict functional recovery of older care recipients after hip fracture. J Adv Nurs 2010;66:2450-9.
21. Ariza-Vega P, Ortiz-Piña M, Kristensen MT, Castellote-Caballero Y, Jiménez-Moleón JJ. High perceived caregiver burden for relatives of patients following hip fracture surgery. Disabil Rehabil 2019;41:311-8.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:115-121
DOI: 10.4274/BMJ.galenos.2024.2024.3-9

Research

Alectinib-induced Non-immune Hemolytic Anemia due to Erythrocyte Membrane Alterations: A Retrospective Evaluation

Alektinib İlişkili Eritrosit Membran Değişikliklerine Bağlı İmmün Olmayan Hemolitik Anemi: Retrospektif Bir Değerlendirme

Emine Gültürk[1], Eyyüp Akkaya[1], Korhan Kapucu[1], Seher Yıldız Tacar[2], Goncagül Akdağ[3], Merve Kahraman Diril[4], Fehmi Hindilerden[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Hematology, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

[3]Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

[4]İstanbul Esenler Gynecology and Children's Diseases Hospital, Clinic of Internal Medicine, İstanbul, Türkiye

ABSTRACT

Objective: The purpose of this study was to evaluate changes in erythrocyte morphology associated with alectinib and resulting hemolytic anemia.

Methods: This was a retrospective analysis of patients with stage IV non-small-cell lung cancer (NSCLC) treated with alectinib. Erythrocyte morphology (by peripheral-blood film evaluation), hemogram, reticulocyte, direct Coombs tests, serum lactate dehydrogenase (LDH), haptoglobin, and indirect bilirubin levels were evaluated. Demographic characteristics of the patients were also collected.

Results: In total, 13 patients (7 women) with a mean age of 52.0±10.5 years were included. Median pre-alectinib hemoglobin level was 12.1 g/dL [minimum (min): 9.4, maximum (max): 16.2 g/dL]. In total, serum hemoglobin was decreased in 8 patients (61.5%) compared with pre-alectinib levels. The average serum hemoglobin level after alectinib use was determined as 11.6 g/dL (min: 8.5 g/dL, max: 13 g/dL). Serum hemoglobin was <10 g/dL in only 3 patients. *De novo* anemia developed in six patients. Peripheral blood examination revealed numerous microspherocanthocytes, some echinocyte, rare fragmented erythrocytes, and generalized anisopoikilocytosis. Serum LDH levels were high in 6 of 13 patients (46.1%) receiving alectinib. Reticulocyte count was high in 10 of 13 patients (76.9%). A decrease in serum haptoglobin was observed in five patients (38.4%). Serum indirect bilirubin was high in two of the patients (15.3%).

Conclusion: Alectinib caused changes in the erythrocyte membrane and non-immune hemolysis in almost all patients using it. Hemolytic anemia was not severe enough to require alectinib dose reduction or discontinuation. Physicians caring for patients receiving alectinib should be alert to hematological changes due to drug use.

Keywords: Alectinib, non-immune hemolytic anemia, erythrocyte membrane changes

ÖZ

Amaç: Çalışmanın amacı, alektinib ile ilişkili eritrosit morfolojisindeki değişiklikleri ve bunun sonucunda ortaya çıkan hemolitik anemiyi değerlendirmekti.

Gereç ve Yöntem: Alektinib ile tedavi edilen evre IV küçük hücreli olmayan akciğer kanseri (KHDAK) hastalarının retrospektif bir analizidir. Eritrosit morfolojisi (periferik kan filmi değerlendirmesi ile), hemogram, retikülosit sayısı, direkt Coombs testleri, serum laktat dehidrogenaz (LDH), haptoglobin, indirekt bilirubin değerlendirildi. Hastaların demografik özellikleri de toplandı.

Bulgular: Toplamda yaş ortalaması 52,0±10,5 yıl olan 13 hasta (7 kadın) dahil edildi. Medyan pre-alektinib hemoglobini 12,1 g/dL [minimum (min): 9,4, maksimum (maks): 16,2 g/dL] idi. Toplamda serum hemoglobini, alektinib öncesi hemoglobin düzeylerine kıyasla 8 hastada (%61,5) azaldı. Alektinib kullanımı sonrası ortalama serum hemoglobin değeri 11,6 g/dL (min: 8,5 g/dL, maks: 13 g/dL) olarak belirlendi. Sadece 3 hastada serum

Address for Correspondence: Emine Gültürk, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Hematology, İstanbul, Türkiye

Phone: +90 505 492 60 59 E-mail: gulturke@yahoo.com.tr ORCID ID: orcid.org/0000-0003-2836-6162

Cite as: Gültürk E, Akkaya E, Kapucu K, Yıldız Tacar S, Akdağ G, Kahraman Diril M, Hindilerden F. Alectinib-induced Non-immune Hemolytic Anemia due to Erythrocyte Membrane Alterations: A Retrospective Evaluation. Med J Bakirkoy 2024;20:115-121

Received: 27.03.2024
Accepted: 26.04.2024

ÖZ

hemoglobin değeri <10 g/dL idi. Altı hastada *de novo* anemisi gelişti. Periferik kan incelemesinde tüm hastalarda çok sayıda mikrosfero-akantosit, bir miktar ekinosit, nadir parçalanmış eritrositler ve jeneralize anizopoikilositoz görüldü. Alektinib tedavisi alan 13 hastanın 6'sında (%46,1) LDH yüksekti. On üç hastanın 10'unda (%76,9) retikülosit yüksekti. Beş hastada (%38,4) serum haptoglobin düzeyinde azalma gözlendi. Hastaların 2'sinde (%15,3) serum indirekt bilirubin yüksekti.

Sonuç: Alektinib kullanan hastaların neredeyse tamamında eritrosit membranında değişikliklere ve immün olmayan hemolizlere neden oldu. Hemolitik anemi, alektinib dozunun azaltılmasını veya kesilmesini gerektirecek kadar ciddi değildi. Alektinib tedavisi gören hastaların tedavisiyle ilgilenen hekimler, ilaç kullanımına bağlı hematolojik değişiklikler konusunda dikkatli olmalıdır.

Anahtar Kelimeler: Alektinib, immün olmayan hemolitik anemi, eritrosit zarı değişiklikleri

INTRODUCTION

Lung cancer is responsible for most cancer-related deaths worldwide (1). Among several types of cancer, non-small-cell lung cancer (NSCLC) constitutes more than 80% of all cases. The most commonly encountered subtypes of NSCLC are adenocarcinoma and squamous carcinoma. Compared with 1975, the 5-year survival rate in lung cancer increased by 9% to 20.5% in 2016 (2). Several factors account for this improvement in prognosis, the most important of which is the advent of targeted therapies and immunotherapy. Recent years have witnessed the discovery and elucidation of several genomic aberrations that are crucial in NSCLC pathogenesis. Almost 30% of patients with NSCLC have one or more of these mutations and rearrangements (3). A number of targeted therapies targeting these mutations enable improved survival, particularly in patients with advanced disease.

Anaplastic lymphoma kinase (ALK) rearrangements have been reported in up to 4.5% of patients with NSCLC (4). First discovered in 2007 (5), an inversion in chromosome 2p produces a fusion gene comprising the *echinoderm microtubule-associated protein-like 4 (EML4)* gene and the *ALK* gene. This fusion gene, in turn, activates the tyrosine kinase domain of the *ALK* gene, resulting in the proliferation of lung epithelial cells (6). The first targeted drug developed to address this important tumorigenic pathway was crizotinib, an ALK tyrosine kinase inhibitor (7). Owing to the observed beneficial effects, crizotinib was recommended as a first-line treatment agent in patients with ALK-rearranged NSCLC. However, with the advent of second- and third-generation ALK tyrosine kinase inhibitors with superior survival rates, better central nervous system penetration, and more acceptable adverse effect profiles, alectinib and ceritinib are now considered as first-line treatment in these patients (8,9).

In a network meta-analysis, low-dose alectinib emerged as having the lowest adverse event risk among all ALK inhibitors (10). This does not mean that alectinib is not without adverse events (11). In the ALEX trial, adverse effects related to alectinib included constipation, liver function abnormalities, anemia (in 26% of the drug users), peripheral edema, myalgia, rash, and bradycardia. Most reported anemia cases were mild, and the median time to anemia development was 3.9 months (12). However, there were no data regarding the nature of alectinib-related anemia. After the publication of the ALEX trial (12), several case reports and series (13-15) reported a type of non-immune hemolytic anemia in patients with NSCLC treated with alectinib. These reports pointed to the development of erythrocyte membrane changes as the culprit triggering extravascular hemolysis in the spleen. Compared with the common use of alectinib, studies characterizing alectinib-related anemia are scarce. Thus, we aimed to report our experience with alectinib-induced non-immune hemolytic anemia.

METHODS

Patients and Setting

This is a retrospective analysis of patients with NSCLC who were treated with alectinib and developed nonimmune hemolytic anemia. The oncology departments of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital and Kartal Dr. Lütfi Kırdar City Hospital participated in the study. The University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision no: 2022-17-01, date: 05.09.2022). We retrospectively screened NSCLC patients with *ALK* gene rearrangements and treated them with alectinib from the electronic hospital database and patient charts between January 2016 and April 2022. All NSCLC patients treated with alectinib were included in the study. Deceased patients at the time of screening and patients with missing data were excluded from the study.

Data Collection

Clinicodemographic characteristics such as age, sex, presence of comorbid conditions, ECOG performance status, disease stage during inclusion in the study, institution of curative-intent chemoradiotherapy, histologic subtype of NSCLC, percentage of ALK, and presence of organ metastases before alectinib treatment. We also performed

laboratory tests (serum hemoglobin concentration, white blood cell count, platelet count) before alectinib treatment. Hemoglobin levels were measured after alectinib treatment. In addition, we performed hemolysis tests and other tests to better elucidate alectinib-related anemia. These tests involved serum hemoglobin concentration, serum vitamin B12, folic acid, and ferritin levels, serum lactate dehydrogenase (LDH), total and direct bilirubin, haptoglobin levels, direct and indirect Coombs tests, reticulocyte count, peripheral smear, and paroxysmal nocturnal hemoglobinuria panel. Response to alectinib therapy was classified as complete or partial response, stable disease, and progression. We also collected data regarding adverse events (AE) related to alectinib use. Common Terminology Criteria for Adverse Events v3.0 was used to grade observed AE as follows: Grade 1, Mild AE; grade 2, Moderate AE; grade 3, Severe AE; grade 4, life-threatening or disabling AE; and grade 5, death related to AE (16).

Statistical Analysis

Categorical variables are reported as numbers and percentages (%). Continuous variables are given as mean ± standard deviation or median [minimum (min) - maximum (max)] depending on the distribution of the variable. The Wilcoxon signed-rank test was used to evaluate the statistical significance of pre- and post- alectinib serum LDH values, and the paired samples t-test was used for comparing serum hemoglobin values. Statistical analyses were performed by processing the data of the patients with the SPSS v22 (IBM, New York) program.

RESULTS

General Characteristics

We obtained data of 13 patients via screening of the hospital database and records of oncology departments. None of the patients were excluded from the study. Overall, 13 patients (7 females) with a mean age of 52.0±10.5 years were included in the study. All patients had stage 4 NSCLC with an adenocarcinoma subtype. All patients had one or more distant organ metastases. The most common organ metastasis was to the bone (9/13), followed by the brain (5/13). Six of 13 patients were administered cytotoxic chemotherapy before the institution of alectinib. In all cases, the chemotherapy regimen involved a carboplatin + taxane combination. Three patients showed a complete response to alectinib therapy, eight patients had a partial response, and one patient had stable disease under alectinib therapy. The mean duration of alectinib use was 26.3±15.7 months. Eight of 13 patients (57.1%) developed at least one AE other than anemia related to alectinib use. All observed AEs were grade 1 or 2. No dose reduction or drug discontinuation was not needed because of AEs. Only one patient (patint number 14) required red blood cell (RBC) transfusion because of anemia during her disease. All patients were alive during data collection for this study. Table 1 shows the demographic and clinical characteristics of the study patients.

Anemia Parameters

Before alectinib treatment, 9 of 13 patients already had anemia. The median pre-alectinib hemoglobin level was 12.1 g/dL (min: 9.4, max: 16.2 g/dL). In total, 8 patients (61.5%) had reduced serum hemoglobin levels compared with pre-alectinib hemoglobin levels. The mean serum hemoglobin level after alectinib use was 11.6 g/dL (min: 8.5 g/dL, max: 13 g/dL). Only three patients had serum hemoglobin values below 10 g/dL. *De novo* anemia developed in 6 of 13 patients (patients nos 2, 4, 6, 8, 10, and 13). There was no statistically significant change in the mean hemoglobin values of patients before and after alectinib use (p=0.091, the paired samples t-test). Table 2 depicts the laboratory values of the patients.

In all patients, except patient 8, peripheral blood film demonstrated numerous microsphero-acanthocytes, some echinocytes, rare fragmented erythrocytes, and general anisopoikilocytosis (Figure 1). Patient number 8 showed no erythrocyte membrane changes but had an iron deficiency anemia morphology. However, her serum ferritin level was within the normal range. In patient 10, the peripheral smear showed normochromic normocytic erythrocytes with rare acanthocytes.

Other Laboratory Studies

Serum LDH levels were elevated before alectinib treatment in 3 of 11 patients (27.2%). With alectinib treatment, 6 of 13 patients (46.1%) had elevated LDH levels. Median serum LDH levels before and during alectinib use were 210 U/L and 203 U/L, respectively (p=0.110, the Wilcoxon signed-rank test). Ten of 13 patients (76.9%) had elevated reticulocyte counts. Direct and indirect Coombs tests were negative in all patients. At the time of evaluation, serum haptoglobin levels were reduced in only 5 patients (38.4%). Serum indirect bilirubin levels were elevated in only 2 of the patients (15.3%).

DISCUSSION

The most salient findings of the present study were as follows: (i) Alectinib led to non-immune hemolytic anemia in all patients who used it. (ii) None of the patients required

Table 1. Demographic and some clinical characteristics of the patients

Patient no	Sex	Age (years)	Comorbid condition	Organ metastasis	Pre-alectinib chemotherapy	Response to alectinib	Adverse events other than anemia	Specific adverse events	Duration of alectinib use (months)
1	Female	47	-	Bone	Yes	Partial	Yes	Increased liver transaminases	29.3
2	Female	61	-	Brain	Yes	Partial	No	-	19.5
3	Male	65	-	Bone	No	Complete	Yes	Nausea	21.8
4	Male	71	Hypertension	Pleura	Yes	Stable disease	Yes	Anemia and increased creatinine	51.7
5	Female	46	Breast cancer	Brain, bone, and pleura	No	Partial	Yes	Leg edema and anemia	40.0
6	Male	52	-	Brain, bone	Yes	Partial	Yes	Anemia, hyperbilirubinemia	28.0
7	Male	52	Hypertension Diabetes mellitus	Bone, pleura	No	-	No	-	0.8
8	Female	61	-	Bone, pleura	No	Partial	Yes	Leg edema, myalgia, and anemia	33.5
9	Male	59	-	Bone, adrenal gland, pleura	No	Partial	Yes	Nausea, Diarrheae	33.5
10	Male	44	-	Bone	Yes	Partial	No	-	39.0
11	Male	52	-	Pleura	No	Partial	No	-	5.2
12	Female	31	-	Brain, adrenal gland, pleura	Yes	Complete	No	-	2.3
13	Female	48	-	Liver	No	Complete	Yes	Nausea, increased liver transaminases, myalgia, and anemia	37.2

Table 2. Laboratory values of patients before and during alectinib use

Patient no	Serum hemoglobin (g/dL)		LDH (U/L)		Reticulocyte count (%)	Haptoglobin (g/L)	Indirect bilirubin (mg/dL)
	Before alectinib	After alectinib	Before alectinib	After alectinib			
1	11.5	12.4	272	289	2.27	1	0.42
2	14.6	10.2	295	251	4.23	0.17	0.9
3	11.9	13.0	163	213	2.47	0.88	0.4
4	12.8	8.5	212	626	2.9	0.05	0.31
5	14.4	12.4	156	199	2.87	0.56	0.33
6	14.1	11.7	213	191	3.01	0.05	1.29
7	9.9	11.0	232	306	0.77	6.01	0.05
8	12.1	9.3	-	221	1.83	1.57	0.07
9	12.4	11.9	-	278	2.27	0.1	0.44
10	16.2	12.9	145	173	1.41	1.4	0.36
11	9.4	10.4	109	150	2.31	1.69	0.20
12	10.4	11.5	197	195	2.19	0.43	0.48
13	12.1	8.5	210	203	5.32	0.1	1.07

Normal reference values for haptoglobin (0.3-2.0 g/L), lactate dehydrogenase (LDH) (135-214 U/L), reticulocyte count (0.2-2%)

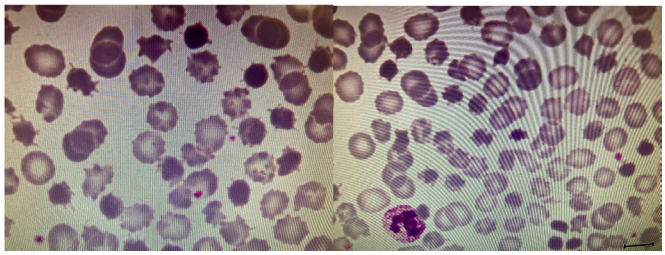

Figure 1. Peripheral blood smear samples showing numerous microsphero-acanthocytes, some echinocyte, rare fragmented erythrocytes, and general anisopoikilocytosis

alectinib dose reduction or cessation due to anemia. (iii) RBC morphological alterations were observed in all patients. (iv) Hemolytic anemia was nonimmune in all alectinib users. (v) The most prominent morphologic change in RBCs was the development of acanthocytosis.

We evaluated the presence and characteristics of anemia in patients with stage IV NSCLC. Our results showed the occurrence of anemia in all alectinib users. In contrast to the universal development of hemolytic anemia in our cohort related to alectinib use, clinical trials reported the development of anemia between 14-22% of patients in whom alectinib was used (12,17). Unfortunately, these trials did not provide details of the anemia type. One case series by Gullapalli et al. (18) reported alectinib-related hemolytic anemia in six patients, but they did not reveal among how many alectinib users they selected these six patients. Kunz et al. (15) conducted a prospective observational study in which they reported the development of reticulocytosis and abnormal erythrocyte morphology with anisocytosis in all 24 patients who were treated with alectinib within 2 weeks of its use. Our results are in agreement with those of the latter authors in that alectinib caused RBC morphologic changes and nonimmune hemolytic anemia in all treated patients.

We report the third largest case series after Kuzich et al. (13) and Kunz et al. (15), in which alectinib-related hemolytic anemia was characterized. To the best of our knowledge, 64 cases have been reported in the literature to date.

Alectinib-induced RBC membrane changes were first described by Kuzich et al. (13). The authors retrospectively evaluated 43 patients with advanced NSCLC and observed marked acanthocytosis, echinocytosis, and/or spheroacanthocytosis in 95% of the alectinib-treated patients. However, anemia developed only in 73% of the patients and was mild to severity. Serum hemoglobin values were <10 g/dL in 38% and <8 g/dL in only 8% of the patients. Kunz et al. (15) found RBC membrane changes in all treated patients. The most commonly encountered morphological abnormality was acathopcytes, followed by echinocyte, spherocytes, dacrocytes, and fragmentocytes. Anemia was present in only 68% of the patients treated with alectinib in Kunz et al. (15). The peripheral blood film of our patients showed widespread acanthocytosis, except in one patient. Among our patients, anemia was present in 61.5% of the patients with alectinib use. However, the *de novo* anemia rate related to alectinib use was 46%. There was no severe anemia, and only two patients had serum hemoglobin levels below 10 g/dL. None of our patients required alectinib dose reduction or discontinuation because of the development of anemia.

The exact mechanism of alectinib-induced alterations in the RBC membrane is yet to be elucidated. However, Kuzich et al. (13) and others (15) showed reduced eosin-5-maleimide staining (EMA) binding in affected patients. This finding, along with apparent morphologic changes, implies that alectinib leads to erythrocyte cytoskeletal changes. Apart from one case by Okumoto et al. (19), all reported alectinib-induced anemia cases in the literature were nonimmune and extravascular. The direct antiglobulin (Coombs) test was consistently found to be negative in reported cases. Okumoto et al. (19) reported alectinib-induced hemolytic anemia, and the Coombs test was negative. Nevertheless, the authors concluded that their case was Coombs-negative immune hemolytic anemia. We believe that the authors actually detected non-immune hemolytic anemia precipitated by alectinib-induced RBC membrane changes but erroneously labeled this as Coombs-negative immune hemolytic anemia. In our cohort, similar to the literature, all patients had negative direct and indirect Coombs tests.

In our study, reticulocyte counts were increased in 76.9% of the patients. The highest reticulocyte count was 4.23%. The results of Kuzich et al. (13) were similar to ours in terms of reticulocyte counts. It was available for seven of their patients (elevated in four), and the maximum value was 3.6%. On the other hand, in the study by Kunz et al. (15), 87.5% of the patients had elevated reticulocyte counts, and the maximum value was 8.3%. In our opinion, the discrepancy between the reticulocyte counts between our results and those by Kunz et al. (15) results from the study design difference. Kunz et al. (15) conducted a prospective study and had the opportunity to prospectively evaluate the patients at monthly intervals after alectinib initiation. Thus, they might have caught the most manifest time of alectinib-induced hemolysis. In contrast, in our evaluation, some patients had been on alectinib treatment for several months. Interestingly, reticulocyte elevation was still evident in three-fourths of our patients, and the counts were somehow smaller compared with those of patients by Kunz et al. (15).

Some limitations of this study deserve mention: First, ours was a retrospective study. Thus, we may have missed some relevant data due to the progress of RBC changes and resultant hemolysis. Second, we did not perform an EMA binding test or other investigations related to ultrastructural changes in the erythrocyte membrane. Thus, we cannot draw any conclusions as to the exact mechanism of the RBC membrane changes that were evident in the light microscopic evaluation. However, studies of some groups mentioned earlier shed some light on the underpinnings of acathocyte development with alectinib use. EMA binging was uniformly diminished, pointing to a possible effect of alectinib on the RBC membrane structure. However, we still do not know by what mechanism alectinib can alter the membrane structure. Third, we cannot determine whether this observed effect of alectinib is specific to alectinib or a class effect. Other studies in the literature have not observed changes in RBCs similar to alectinib with the use of other ALK inhibitors such as crizotinib, brigatinib, and lorlatinib (15). Lastly, we cannot determine whether alectinib-related changes in RBC membranes are temporary because all of our patients were still using their alectinib treatments at the time of the evaluation. However, other researchers have reported that RBC membrane changes were corrected upon discontinuation of alectinib use (15).

CONCLUSION

In conclusion, in this third-largest study regarding the effects of alectinib on RBCs, we showed that alectinib caused erythrocyte membrane changes and nonimmune hemolyses in almost all patients who used it. Hemolytic anemia was not severe, necessitating drug dose reduction or discontinuation. However, it is of utmost importance to know alectinib-related hematologic changes beforehand so that lengthy and expensive studies can be undertaken to investigate the cause of anemia and hemolysis in alectinib-treated patients.

ETHICS

Ethics Committee Approval: The University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (decision no: 2022-17-01, date: 05.09.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.G., S.Y.T., G.A., F.H., Concept: E.G., Design: E.G., Data Collection or Processing: E.G., E.A., K.K., S.Y.T., G.A., M.K.D., Analysis or Interpretation: E.G., Literature Search: E.G., Writing: E.G.

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

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

REFERENCES

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2019;5:1749-68.
2. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. Contemp Oncol (Pozn) 2021;25:45-52.
3. Chen J, Xu C, Lv J, Lu W, Zhang Y, Wang D, et al. Clinical characteristics and targeted therapy of different gene fusions in non-small cell lung cancer: a narrative review. Transl Lung Cancer Res 2023;12:895-908.
4. El Yacoubi H, Sow ML, Kettani F, Gamra L, Mestari A, Jabri L, et al. Frequency of anaplastic lymphoma kinase rearrangements in Moroccan patients with non small cell lung cancer: a multi-institutional national retrospective study. BMC Cancer 2020;20:479.
5. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
6. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. World J Clin Oncol 2021;12:217-37.
7. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011-9.
8. McCusker MG, Russo A, Scilla KA, Mehra R, Rolfo C. How I treat ALK-positive non-small cell lung cancer. ESMO Open 2019;4:e000524.
9. Chazan G, Solomon BJ. Optimal first-line treatment for metastatic ALK+ non-small cell lung cancer-a narrative review. Transl Lung Cancer Res 2023;12:369-78.
10. Chuang CH, Chen HL, Chang HM, Tsai YC, Wu KL, Chen IH, et al. Systematic Review and Network Meta-Analysis of Anaplastic Lymphoma Kinase (ALK) Inhibitors for Treatment-Naive ALK-Positive Lung Cancer. Cancers (Basel) 2021;13:1966.
11. Dziadziuszko R, Peters S, Ruf T, Cardona A, Guerini E, Kurtsikidze N, et al. Clinical experience and management of adverse events in patients with advanced ALK-positive non-small-cell lung cancer receiving alectinib. ESMO Open 2022;7:100612.
12. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:829-38.
13. Kuzich JA, Heynemann S, Geoghegan N, Evelyn C, O'Mahoney S, Wilson S, et al. Alectinib induces marked red cell spheroacanthocytosis in a near-ubiquitous fashion and is associated with reduced eosin-5-maleimide binding. Pathology 2021;53:608-12.
14. El Sayed R, Tehfe M, Blais N. Successful Treatment with Brigatinib after Alectinib-Induced Hemolytic Anemia in Patients with

Metastatic Lung Adenocarcinoma-A Case Series. Curr Oncol 2022;30:518-28.

15. Kunz J, Wiedemann C, Grosch H, Kriegsmann K, Gryzik S, Felden J, et al. Early Development of Ubiquitous Acanthocytosis and Extravascular Hemolysis in Lung Cancer Patients Receiving Alectinib. Cancers (Basel) 2022;14:2720.
16. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS, March 31, 2003, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf.
17. Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, et al. Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study. J Thorac Oncol 2019;14:1233-43.
18. Gullapalli V, Xu W, Lewis CR, Anazodo A, Gerber GK. A multi-centre case series of alectinib-related erythrocyte membrane changes and associated haemolysis. J Hematop 2021;14:131–6.
19. Okumoto J, Sakamoto S, Masuda T, Yamaguchi K, Horimasu Y, Miyamoto S, et al. Alectinib-induced Immune Hemolytic Anemia in a Patient with Lung Adenocarcinoma. Intern Med 2021;60:611-15.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:122-128
DOI: 10.4274/BMJ.galenos.2024.2024.2-14

Research

Laboratory Findings in Atrial Fibrillation-related Stroke Patients Underwent Reperfusion Treatment

Reperfüzyon Tedavisi Uygulanan Atrial Fibrilasyon Tanılı İnme Hastalarında Laboratuvar Bulgularının İncelenmesi

Hacı Ali Erdoğan, İbrahim Acır, Vildan Yayla

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye

ABSTRACT

Objective: Stroke is a prominent contributor to both mortality and disability worldwide, with most affected individuals suffering from acute ischemic strokes. Atrial fibrillation (AF) is one of the most known cardiac arrhythmias and increases the risk of ischemic stroke fivefold. Studies regarding laboratory findings in patients with acute AF-related stroke are limited. Blood biomarkers and laboratory findings can provide additional information on stroke severity, potential underlying causes, and treatment response. Our aim is to discuss laboratory findings and biomarkers in patients with acute stroke treated with mechanical thrombectomy (MT) and intravenous thrombolysis (IV r-tPA).

Methods: A total of 219 acute stroke patients were treated with IV r-tPA and/or MT. Patients with known AF or those diagnosed during follow-up were classified as AF (+), whereas others were classified as AF (-).

Results: C-reactive protein, monocytes, and neutrophil/lymphocyte ratio values were significantly higher in both groups on day 7. Some laboratory parameters (white blood cell, red blood cell and glomerular filtration rate) showed significant differences between the two groups. Additionally, we found that leukocyte and neutrophil values were elevated only in the AF (+) group on day 7. In the AF (+) group, the left atrial diameter on transthoracic echocardiography was >40 mm, and troponin levels were high.

Conclusion: Laboratory findings in patients with AF receiving acute stroke treatment can provide additional information about many clinical events related to stroke. These findings and biomarkers can provide more details on stroke severity, underlying causes, and treatment effectiveness. Because there is limited research on laboratory findings in strokes related to AF, our study can provide additional contributions to this important area.

Keywords: Stroke, atrial fibrillation, laboratory findings, stroke treatment

ÖZ

Amaç: İnme, dünyada ölüm ve sakatlığın en önemli nedenleriden biridir. İnme hastalarının çoğunluğu akut iskemik inme olgularıdır. Atriyal fibrilasyon (AF) en sık görülen kardiyak aritmilerden biridir ve iskemik inme riskini beş kat artırır. Akut AF ile ilişkili inme hastalarında laboratuvar bulguları ile ilgili çalışmalar sınırlıdır. Kan biyobelirteçleri ve laboratuvar bulguları, inme şiddeti, potansiyel ana nedenler ve tedavi yanıtının değerlendirilmesi hakkında ek bilgiler sağlayabilir. Amacımız, mekanik trombektomi (MT) ve intravenöz tromboliz (IV r-tPA) tedavisi uygulanan akut inme hastalarında laboratuvar bulgularını ve biyobelirteçleri tartışmaktır.

Gereç ve Yöntem: Toplamda 219 hastaya, IV r-tPA ve/veya MT ile akut inme tedavisi uygulandı. AF'yi olan veya takip sırasında tespit edilen hastalar AF (+) olarak değerlendirildi, diğerleri AF (-) olarak sınıflandırıldı.

Bulgular: C-reaktif protein, monositler ve nötrofil/lenfosit oranı değerlerini her iki grupta da 7. günde anlamlı derecede yüksek tespit edildi. Bazı laboratuvar parametleri (beyaz kan hücresi, kırmızı kan hücresi ve glomerül filtrasyon hızı) her iki grup arasında anlamlı farklılık gösteriyordu. Ayrıca, lökosit ve nötrofil değerlerinin sadece AF (+) grubunda 7. günde yüksek olduğunu bulduk. AF (+) grupta sol atriyum çapı transtorasik ekokardiyografide >40 mm ve troponin düzeyi yüksekti.

Sonuç: Akut inme tedavisi alan AF'li hastalarda laboratuvar bulguları inme bağlantılı birçok klinik olay hakkında ek bilgi sağlayabilir. Bu bulgu ve biyobelirteçler inmenin şiddeti, potansiyel temel nedenleri ve tedavinin etkinliğinin değerlendirilmesi hakkında daha fazla detay sunabilir. Ayrıca AF'ye bağlı inmelerde laboratuvar bulguları ilgili sınırlı çalışma olduğundan çalışmamız bu önemli konuda ek katkılar sağlayabilir.

Anahtar Kelimeler: İnme, atriyal fibrilasyon, laboratuvar bulguları, reperfüzyon tedavisi

Address for Correspondence: Hacı Ali Erdoğan, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye
Phone: +90 505 684 16 18 E-mail: drhaciali@gmail.com ORCID ID: orcid.org/0000-0001-6870-4002

Cite as: Erdoğan HA, Acır İ, Yayla V. Laboratory Findings in Atrial Fibrillation-related Stroke Patients Underwent Reperfusion Treatment. Med J Bakirkoy 2024;20:122-128

Received: 08.03.2024
Accepted: 17.05.2024

INTRODUCTION

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia linked with elevated susceptibility to stroke. Patients with AF who experience an acute stroke often require prompt medical intervention to minimize the extent of neurological damage and improve outcomes (1). In addition to the clinical management of stroke, understanding the laboratory findings in patients with AF undergoing therapy for acute stroke is essential for optimizing patient management and improving outcomes. By evaluating coagulation parameters, markers of inflammation, cardiac biomarkers, and other relevant laboratory tests, clinicians can tailor treatment plans to individual patients, enhance risk stratification, and monitor treatment response. In addition, these findings can contribute to the ongoing research and development of novel diagnostic tools and therapeutic strategies for AF-related stroke.

This study aims to discuss the laboratory findings commonly observed in patients with AF undergoing therapy for acute stroke and provide valuable insights into the comprehensive care of patients with AF and acute stroke, ultimately leading to improved patient outcomes.

METHODS

A total of 219 patients who underwent reperfusion therapies, such as intravenous thrombolysis (IV r-tPA) and/or mechanical thrombectomy (MT), were analyzed. Patients diagnosed with AF during either initial assessment or subsequent follow-up were categorized as AF positive (+), whereas those without such diagnosis were designated as AF negative (-). Patients ineligible for IV r-tPA and MT because of contraindications, and those with valvular AF or undergoing antibiotic treatment, were excluded from the study. The demographic and clinical profiles of patients were assessed. Transthoracic echocardiography (TTE) was performed in all patients. Laboratory results were reported, and those with and without AF were compared. Laboratory values were obtained on admission and on day 7 following acute stroke therapy. Changes in laboratory findings were recorded. University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics committee approval was obtained (decision no: 2023-15-06, date: 07.08.2023). Patient consent form was not required in this study.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics. Normality was assessed using the Shapiro-Wilk test. Numerical variables are expressed as mean ± standard deviation or median (minimum-maximum) for normally or non-normally distributed data, respectively. Categorical variables are presented as frequencies and percentages. Student's t-test or Mann-Whitney U test compared numerical variables between the two groups. ANOVA or Kruskal-Wallis H tests were used for three or more groups. Chi-square, Yates correction, and Fisher's Exact tests were used to compare categorical data. Pearson or Spearman correlation analysis examined the numerical variable relationships. A significance level of $p<0.05$ was considered significant.

RESULTS

The average age of the overall population was 68.3 years, whereas the average age of individuals with AF was 73.8 years and that of individuals without AF was 64.8 years. There was a significant difference in age between the AF and non-AF groups ($p<0.001$). The distribution of gender was also significantly different between the two groups, with a higher proportion of women in the AF group (58.9%) than in the non-AF group (29.5%, $p<0.001$). Comorbid diseases such as diabetes mellitus (DM) and coronary artery disease (CAD) showed significant differences between the AF and non-AF groups (Table 1).

The ejection fraction (EF) was evaluated, and no significant difference was found between the AF and non-AF groups ($p=0.100$). However, the left atrial diameter showed a significant difference, with a higher proportion of individuals having a left atrial diameter greater than 40 mm in the AF group than in the non-AF group ($p<0.001$). The acute stroke treatment methods also differed significantly between the two groups, with a higher proportion of individuals in the AF group receiving MT ($p=0.001$) (Table 2).

Several laboratory parameters showed significant differences between the AF and non-AF groups. These included white blood cell count ($p=0.004$), platelet count ($p=0.001$), red blood cell count ($p=0.020$), neutrophil count ($p=0.016$), monocyte count ($p=0.018$), glomerular filtration rate (GFR), and troponin levels ($p=0.025$). Uric acid, C-reactive protein (CRP), albumin, and various other biomarkers did not show significant differences between the two groups (Table 3).

The changes in laboratory findings between the baseline and 7th day measurements for the AF-positive and AF-negative groups was presented Table 4. CRP levels significantly increased in both groups ($p<0.001$), indicating an inflammatory response. Albumin levels significantly decreased in both groups ($p<0.001$), suggesting a decrease in protein synthesis. White blood cell count and neutrophil count significantly increased in AF (+) group on the 7th day.

Table 1. Demographic data of patients

Variables	All population n=219	AF		p-value
		Present n=90	Absent n=129	
Age, year	68.3±15.2	73.8±13.9	64.8±15.6	<0.001*
Gender, n (%)				
Female	91 (41.6)	53 (58.9)	38 (29.5)	<0.001*
Male	128 (58.4)	37 (41.1)	91 (70.5)	
Comorbidities, n (%)				
Absent	40 (18.3)	6 (6.7)	34 (26.4)	<0.001*
Present	179 (81.7)	84 (93.3)	95 (73.6)	
DM	65 (29.1)	34 (37.0)	31(23.7)	0.037*
HT	122 (54.7)	56 (60.9)	66 (50.4)	0.121
HL	16 (7.2)	7 (7.6)	9 (6.9)	0.998
CAD	65 (29.1)	35 (38.0)	30 (22.9)	0.017*
CRF	33 (14.8)	15 (16.3)	18 (13.7)	0.702
CVD	1 (0.4)	1 (1.1)	0	0.859
Malignancy	2 (0.9)	1 (1.1)	1 (0.8)	0.999
Other	67 (30.5)	34 (38.0)	32 (25.2)	0.054
Smoke (pack/year), n (%)				
None	121 (55.2)	61 (67.4)	60 (46.6)	0.002*
Ex-smoker	11 (4.9)	2 (2.2)	9 (6.9)	
Smoker	40 (18.4)	8 (8.7)	32 (25.2)	
Unknown	47 (21.5)	19 (21.7)	28 (21.4)	

Numerical variables were expressed as mean ± standard deviation or median (minimum-maximum). Categorical variables shown as numbers (%).
*p<0.05 indicates statistical significance. AF: Atrial fibrillation, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease, CRF: Chronic renal failure, CVD: Cardiovascular disease.

Table 2. Clinical variables

Variables	All population n=219	AF		p-value
		Present n=90	Absent n=129	
EF, n (%)				
45-60%	131 (59.8)	49 (54.4)	82 (63.5)	0.100
30-45%	24 (10.9)	14 (15.5)	10 (7.7)	
<30%	13 (5.9)	3 (3.3)	10 (7.7)	
Unknown	51 (23.2)	24 (26.6)	27 (20.9)	
Left atrial diameter, n (%)				
<40	79 (36.0)	18 (20.0)	61 (47.2)	<0.001*
>40	72 (32.8)	42 (46.6)	30 (23.2)	
Unknown	68 (31.0)	30 (33.3)	38 (29.4)	
Acute stroke therapies, n (%)				
Thrombolysis (TPA)	82 (37.4)	20 (22.2)	62 (48.0)	0.001*
Thrombectomy	108 (49.3)	56 (62.2)	52 (40.3)	
TPA bolus + thrombectomy	5 (2.2)	3 (3.3)	2 (1.5)	
TPA + thrombectomy	22 (10.0)	10 (11.1)	12 (9.3)	
Thrombectomy + stent	2 (0.9)	1 (1.1)	1 (0.7)	

Numerical variables were expressed as mean ± standard deviation or median (minimum-maximum). Categorical variables shown as numbers (%).
*p<0.05 indicates statistical significance. AF: Atrial fibrillation, EF: Ejection fraction

Table 3. Laboratory findings

Variables	All population n=219	AF		p-value
		Present n=90	Absent n=129	
Admission				
GFR	79.9±24.5	75.8±23.8	82.9±24.6	0.034*
Uric acide	5.9±1.8	6.0±2.0	5.8±1.7	0.315
CRP	6.4 (0-240)	6.9 (0-240)	6.2 (0-237)	0.450
Albumin	37.6±4.8	37.2±4.8	37.8±4.8	0.366
WBC	9.2 (3.4-24.3)	8.7 (4.4-15)	9.6 (3.4-24.3)	0.004*
PLT	239 (97-703)	213 (97-481)	253 (127-703)	0.001*
RBC	4.5±0.6	4.4±0.6	4.6±0.6	0.020*
RDW	14.2±1.6	14.4±1.6	14.0±1.7	0.048*
Neutrophil	6.1 (0.6-22.4)	5.5 (1.8-11.3)	6.4 (0.6-22.4)	0.016*
Lymphocyte	1.9 (0.3-7)	1.9 (0.3-5.1)	1.9 (0.5-7)	0.385
Monocyte	0.7 (0.2-10.5)	0.6 (0.2-10.5)	0.7 (0.2-2.5)	0.018*
Folate	8.5 (3.2-460)	8.1 (3.2-22.4)	8.8 (3.2-23.4)	0.680
Vitamin B12	220 (41-1500)	236 (60-928)	201 (41-1500)	0.142
Troponin	9 (0-11723)	12 (0-10177)	8.5 (0-11723)	0.025*
APTT	32 (17.8-200)	32 (21.6-64.5)	32 (17.8-200)	0.996
INR	1.1 (0.8-10.2)	1.1 (0.9-2.9)	1.1 (0.8-10.2)	0.102
HDL	41.3 (18.8-279)	41.1 (20-78)	42 (18.8-279)	0.907
LDL	121 (35-390)	114 (35-277)	124.6 (36-390)	0.161
TG	104 (28-436)	102 (28-275)	107 (45-436)	0.066
NLR	3.3 (0.3-36.7)	3 (0.8-36.7)	3.6 (0.3-22.7)	0.350
PLR	125.7 (37.3-660)	116.5 (38.9-531.3)	129.2 (37.3-660)	0.381
MLR	0.4 (0.1-2.8)	0.3 (0.2-2.8)	0.4 (0.1-1.7)	0.698
Fibrinogen	354 (0.7-968)	359 (266-968)	346 (0.7-615)	0.189
NSE	15.1 (0.1-77.7)	14.2 (8-43)	15.5 (0.1-77.7)	0.968
D-D	0.7 (0.1-7.1)	0.6 (0.2-2.8)	0.9 (0.1-7.1)	0.373
Seventh day				
CRP	83 (0-512)	78 (0-512)	87.5 (0-387)	0.685
ALB	29.6 (17.2-277)	28.6 (19.8-39)	31.2 (17.2-277)	0.085
WBC	10 (4-32.8)	10.2 (4.2-19.6)	9.8 (4-32.8)	0.879
PLT	245 (10.1-638)	241 (64-524)	2489 (10.1-638)	0.015*
RBC	5.6±16.1	4.0±0.7	4.2±0.7	0.018*
RDW	14.3±2.0	14.5±1.7	14.1±2.2	0.184
Neutrophil	7.4 (2.5-88.7)	7.8 (2.7-16.9)	6.9 (2.5-88.7)	0.610
Lymphocyte	1.4 (0.1-9.7)	1.3 (0.3-4.2)	1.5 (0.1-9.7)	0.075
Monocyte	0.8 (0-3.5)	0.8 (0.1-1.8)	0.8 (0-3.5)	0.551
NLR	4.8 (1-158.4)	6.1 (1-29.7)	4.4 (1.1-158.4)	0.111
PLR	168 (1.2-1601.5)	167.6 (53.4-591.7)	168.9 (1.2-1601.5)	0.807
MLR	0.5 (0.1-5.6)	0.6 (0.2-2.7)	0.5 (0.1-5.6)	0.093
Fibrinogen	322 (147-799)	383.5 (160-544)	310.5 (147-799)	0.104
NSE	14.4 (0.1-125.9)	18.4 (3.3-60.9)	10.5 (0.1-125.9)	0.107
D-D	1 (0.1-7.5)	1 (0.3-5.6)	1.1 (0.1-7.5)	0.802

Numerical variables were expressed as mean ± standard deviation or median (minimum-maximum). Categorical variables shown as numbers (%).
*p<0.05 indicates statistical significance. AF: Atrial fibrillation, GFR: Glomerular filtration rate, CRP: C-reactive protein, WBC: White blood cell, PLT: Platelet, RBC: Red blood cell, RDW: Red Blood Cell distribution width, APTT: Activated partial thromboplastin time, INR: International normalized ratio, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglycerides, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, NSE: Neuron-specific enolase, D-D: D-Dimer

Table 4. Changes in laboratory findings at admission and on day seven

Variables	AF (+) n=90		p-value	AF (-) n=129		p-value	Δp
	Admission	7th day		Admission	7th day		
CRP	6.9 (0-240)	78 (0-512)	<0.001*	6.2 (0-237)	87.5 (0-387)	<0.001*	0.507
Albumin	37.2±4.8	28.6 (19.8-39)	<0.001*	37.8±4.8	31.2 (17.2-277)	<0.001*	0.217
WBC	8.7 (4.4-15)	10.2 (4.2-19.6)	<0.001*	9.6 (3.4-24.3)	9.8 (4-32.8)	0.829	0.043*
PLT	213 (97-481)	241 (64-524)	0.097	253 (127-703)	248.5 (10.1-638)	0.994	0.489
RBC	4.4±0.6	4.0±0.7	<0.001*	4.6±0.6	4.2±0.7	<0.001*	0.402
RDW	14.4±1.6	14.5±1.7	0.528	14.0±1.7	14.1±2.2	0.185	0.565
Neutrophil	5.5 (1.8-11.3)	7.8 (2.7-16.9)	<0.001*	6.4 (0.6-22.4)	6.9 (2.5-88.7)	0.581	0.041*
Lymphocyte	1.9 (0.3-5.1)	1.3 (0.3-4.2)	<0.001*	1.9 (0.5-7)	1.5 (0.1-9.7)	0.009*	0.439
Monocyte	0.6 (0.2-10.5)	0.8 (0.1-1.8)	<0.001*	0.7 (0.2-2.5)	0.8 (0-3.5)	0.008*	0.066
NLR	3 (0.8-36.7)	6.1 (1-29.7)	<0.001*	3.6 (0.3-22.7)	4.4 (1.1-158.4)	0.044*	0.915
PLR	116.5 (38.9-531.3)	167.6 (53.4-591.7)	<0.001*	129.2 (37.3-660)	168.9 (1.2-1601.5)	0.008*	0.883
MLR	0.3(0.2-2.8)	0.6 (0.2-2.7)	<0.001*	0.4 (0.1-1.7)	0.5 (0.1-5.6)	<0.001*	0.384

Numerical variables were expressed as mean ± standard deviation or mean ± standard deviation. Categorical variables shown as numbers (%).
*p<0.05 indicates statistical significance.
Δp: Changes in laboratory findings show the difference in terms of the presence of AF. AF: Atrial fibrillation, CRP: C-reactive protein, WBC: White blood cell, PLT: Platelet, RBC: Red blood cell, RDW: Red Blood Cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio

DISCUSSION

AF is the most frequent cardiac arrhythmia and a risk indicator for ischemic stroke, with a prevalence of 1% (2,3). AF may lead to reduced cerebral perfusion, increased stroke severity, and chronic cerebral white matter damage (4). Notably, this arrhythmia is more common in the elderly, females, and people of Caucasian descent (3). Our findings are consistent with those of previous research, with a higher mean age and a higher proportion of female patients in the AF (+) group. Previous studies have reported that comorbid diseases are more frequent in AF (+) patients and that comorbidity negatively affects the prognosis (5). The most common comorbid diseases are hypertension (HT), CAD, chronic renal failure, heart failure, and obesity (6). Consistent with previous studies, comorbid diseases were more common in our AF (+) group. DM and CAD were the most common comorbid diseases in AF (+) patients. However, there was no information about HT between the groups.

TTE allows noninvasive examination of cardiac structures and functions. Therefore, routine TTE examination is recommended in patients with acute ischemic stroke to exclude possible cardioembolic causes (7). AFFIRM and other studies found no correlation between EF and the presence of AF. However, it was found that left atrial enlargement is correlated with AF (8). We performed TTE on all patients. Consistent with the literature, no significant difference was found between the patient groups in terms of EF. However, the diameter of the left atrium showed a significant difference, with a higher proportion of individuals having a left atrium diameter greater than 40 mm in the AF group than in the non-AF group. IV r-tPA and/or MT is recommended for eligible ischemic stroke patients with or without AF in the hyperacute period. Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI studies revealed that IV r-tPA failed in 50% of patients with strokes related to AF, necessitating the application of MT in these cases (9). Smaal et al. (10) reported that MT was mostly applied to patients with AF. Likewise, we also found that the rate of MT was higher in AF (+) than AF (-) patients. However, the IV r-tPA treatment rate was high in AF (-) patients.

The inflammatory response plays an important role in the pathophysiology of acute ischemic stroke (11). Secretion of inflammatory mediators is limited in normal brain tissue.

Cessation of blood flow after acute ischemia induces secretion of proinflammatory cytokines and immune cells (12). In studies, it was found that an increase in leukocyte and neutrophil counts is correlated with infarct volume and stroke severity (12). However, studies on leukocyte, neutrophil, and other blood biochemistry values in AF-related strokes are limited. Kneihsl et al. (13) did not find any differences between AF-related stroke and other patient groups in terms of blood glucose, platelet count, hemoglobin, and CRP levels. We found that leukocytes, neutrophils, monocytes, platelet levels, and GFR were significantly lower in the AF (+) group at admission. As mentioned above, acute ischemic stroke-induced inflammation and the rate of inflammation are directly related to stroke volume. After acute treatment of stroke and regression of clinical signs, inflammatory biomarker levels will decrease. CRP and erythrocyte sedimentation rate can provide insights into the inflammatory response associated with stroke and AF. Increased levels of these markers may suggest an ongoing inflammatory process that can contribute to stroke severity and poorer outcomes. However, there are also studies reporting that CRP levels may be normal in stroke patients and are not predictive of prognosis (14). We did not detect any significant difference at admission and on 7th day CRP values between the patient groups. However, CRP, monocytes, and neutrophil/lymphocyte ratio values were significantly higher on the 7th day in both groups. In addition, we found that leukocyte and neurophil values were higher only in the AF (+) group on 7th day. We may speculate that the inflammatory response is similar in all acute ischemic stroke patients at admission, but over time, inflammation is more pronounced in AF-related stroke patients. Because cardioembolic strokes related to AF are more severe and the inflammation rate was high in these groups. Follow-up of the level of inflammatory biomarkers at regular intervals may help us to determine inflammation and predict clinical improvement. For this speculation, more randomized controlled studies are needed.

Cardiac biomarkers, including troponin and brain natriuretic peptide (BNP) can help identify myocardial injury and cardiac dysfunction, which may further complicate the management of patients with AF and acute stroke (15). Llombart et al. (16) found higher levels of natriuretic peptides [N-terminal pro-brain natriuretic peptide (NT-proBNP) and BNP] in cardioembolic strokes. Similarly, Kneihsl et al. (13) found high levels of NT-proBNP and D-dimer and low levels of antithrombin-III in AF-related strokes. Isenegger et al. (17) found that high D-dimer levels may predict cardioembolic stroke. We did not detect any differences in D-dimer and fibrinogen levels between both groups at admission and 7th day. In our study, only troponin was evaluated as a cardiac biomarker. At admission, troponin levels were significantly higher in the AF (+) group. This situation indirectly suggests that cardiac pathologies are more common in AF (+) patients. Because of logistical reasons, natriuretic peptide levels and BNP could not be measured in our study.

Considering these findings, we believe that more studies are needed to use blood biomarkers to detect AF-related strokes and to determine the prognosis.

Because our study was retrospective, small, and non-controlled, we did not evaluate laboratory findings in the MT and IV r-tPA groups regardless of AF, and some biomarkers were not included in this study. These issues are the limitations of our study.

CONCLUSION

Laboratory investigations in patients with AF undergoing therapy for acute stroke provide insights into various aspects of the disease and its management. In addition, these findings and biomarkers may provide additional information about stroke severity, potential underlying causes, and evaluation of treatment response. In the literature, studies on laboratory findings in strokes due to AF are limited, and our study may provide an additional contribution to this important topic.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics committee approval was obtained (decision no: 2023-15-06, date: 07.08.2023).

Informed Consent: Patient consent form was not required in this study.

Authorship Contributions

Surgical and Medical Practices: H.A.E., Concept: H.A.E., V.Y., Design: H.A.E., V.Y., Data Collection or Processing: İ.A., Analysis or Interpretation: İ.A., Literature Search: İ.A., Writing: H.A.E.

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

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

REFERENCES

1. Bordignon S, Chiara Corti M, Bilato C. Atrial Fibrillation Associated with Heart Failure, Stroke and Mortality. J Atr Fibrillation 2012;5:467.
2. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010;123:638-645.

3. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995;155:469-73.
4. de Leeuw FE, de Groot JC, Oudkerk M, Kors JA, Hofman A, van Gijn J, et al. Atrial fibrillation and the risk of cerebral white matter lesions. Neurology 2000;54:1795-801.
5. Chamberlain AM, Alonso A, Gersh BJ, Manemann SM, Killian JM, Weston SA, et al. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: A population-based study. Am Heart J 2017;185:74-8.
6. Jani BD, Nicholl BI, McQueenie R, Connelly DT, Hanlon P, Gallacher KI, et al. Multimorbidity and co-morbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. Europace 2018;20:329-36.
7. Troughton RW, Asher CR, Klein AL. The role of echocardiography in atrial fibrillation and cardioversion. Heart. 2003;89:1447-54.
8. Olshansky B, Heller EN, Mitchell LB, Chandler M, Slater W, Green M, et al. Are transthoracic echocardiographic parameters associated with atrial fibrillation recurrence or stroke? Results from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. J Am Coll Cardiol 2005;45:2026-33.
9. Shi ZS, Loh Y, Walker G, Duckwiler GR; MERCI and Multi MERCI Investigators. Endovascular thrombectomy for acute ischemic stroke in failed intravenous tissue plasminogen activator versus non-intravenous tissue plasminogen activator patients: revascularization and outcomes stratified by the site of arterial occlusions. Stroke 2010;41:1185-92.
10. Smaal JA, de Ridder IR, Heshmatollah A, van Zwam WH, Dippel D, Majoie CB, et al. Effect of atrial fibrillation on endovascular thrombectomy for acute ischemic stroke. A meta-analysis of individual patient data from six randomised trials: Results from the HERMES collaboration. Eur Stroke J 2020;5(3):245-51.
11. Wang Q, Tang XN, Yenari MA. The inflammatory response in stroke. J Neuroimmunol 2007;184:53-68.
12. Chamorro A, Hallenbeck J. The harms and benefits of inflammatory and immune responses in vascular disease. Stroke 2006;37:291-3.
13. Kneihsl M, Gattringer T, Bisping E, Scherr D, Raggam R, Mangge H, et al. Blood Biomarkers of Heart Failure and Hypercoagulation to Identify Atrial Fibrillation-Related Stroke. Stroke 2019;50:2223-6.
14. Di Napoli M, Di Gianfilippo G, Sollecito A, Bocola V. C-reactive protein and outcome after first-ever ischemic stroke. Stroke 2000;31:238-9.
15. Oikonomou E, Zografos T, Papamikroulis GA, Siasos G, Vogiatzi G, Theofilis P, et al. Biomarkers in Atrial Fibrillation and Heart Failure. Curr Med Chem 2019;26:873-87.
16. Llombart V, Antolin-Fontes A, Bustamante A, Giralt D, Rost NS, Furie K, et al. B-type natriuretic peptides help in cardioembolic stroke diagnosis: pooled data meta-analysis. Stroke 2015;46:1187-95.
17. Isenegger J, Meier N, Lämmle B, Alberio L, Fischer U, Nedeltchev K, et al. D-dimers predict stroke subtype when assessed early. Cerebrovasc Dis 2010;29:82-6.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:129-135
DOI: 10.4274/BMJ.galenos.2024.2024.2-13

Research

What is Gestational Diabetes Mellitus Awareness in Pregnant Women: A Survey Study

Gebelerde Gestasyonel Diyabet Farkındalığının Araştırılması: Anket Çalışması

Seda Tan, Akif Bayyiğit

University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Internal Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Gestational diabetes mellitus (GDM) is an increasing problem in our present day. It is important to increase the awareness of pregnant women regarding this issue for compliance in diagnosis, follow-up, and treatment processes. The purpose of the present study was to evaluate the awareness of GDM and its complications and the approach to the oral glucose tolerance test (OGTT) in pregnant women.

Methods: Fifty patients with GDM or pre-gestational diabetes mellitus (PGDM) after 24 weeks of gestation and 250 patients without GDM and PGDM history were evaluated. A questionnaire on GDM and its complications, consisting of 18 questions, was administered to the groups.

Results: The mean obesity rate was higher (p=0.0001), body mass index was higher (p=0.0001), and a family history of diabetes was found to be more common (p=0.0001) in the group of pregnant women with GDM and PGDM. The rate of correct answers to the questions was 65% in all patients. The awareness level was found to be higher in those who had higher educational status (p=0.0001), those with higher income levels (p=0.0001), and smokers (p=0.03). OGTT rejection was found with a higher rate among those who thought that OGTT would harm the pregnancy and fetus among the pregnant women who did not have diabetes before the 24th gestational week (p=0.006).

Conclusion: Although the awareness of pregnant women regarding GDM was not at an insufficient level, there was a lack of knowledge regarding some issues.

Keywords: Gestational diabetes, diabetes complications, pregnancy complications

ÖZ

Amaç: Gestasyonel diabetes mellitus (GDM) günümüzde giderek artan bir sorundur. Gebelerin bu konudaki farkındalıklarının artırılması tanı, takip ve tedavi süreçlerine uyum açısından önemlidir. Bu çalışmanın amacı gebelerde GDM ve komplikasyonlarının farkındalığını ve oral glukoz tolerans testine (OGTT) yaklaşımı değerlendirmektir.

Gereç ve Yöntem: 24. gebelik haftasından sonra GDM veya pre-gestasyonel diabetes mellitus (PGDM) tanısı alan 50 hasta ile GDM ve PGDM öyküsü olmayan 250 hasta değerlendirildi. Gruplara GDM ve komplikasyonları hakkında 18 sorudan oluşan bir anket uygulandı.

Bulgular: GDM ve PGDM öyküsü olan gebelerde ortalama obezite oranı daha yüksek (p=0,0001), vücut kitle indeksi daha yüksek (p=0,0001) ve ailede diyabet öyküsü daha yaygın (p=0,0001) bulundu. Tüm hastalarda sorulara doğru yanıt verme oranı %65'tir. Eğitim düzeyi yüksek olanlarda (p=0,0001), gelir düzeyi yüksek olanlarda (p=0,0001) ve sigara içenlerde (p=0,03) farkındalık düzeyi daha yüksek bulunmuştur. Diyabeti olmayan gebeler arasında 24. gebelik haftasından önce OGTT'nin gebeliğe ve fetüse zarar vereceğini düşünenler arasında OGTT reddi daha yüksek oranda bulunmuştur (p=0,006).

Sonuç: Gebelerin GDM ile ilgili farkındalıkları yetersiz düzeyde olmamakla birlikte bazı konularda bilgi eksikliği olduğu saptanmıştır.

Anahtar Kelimeler: Gestasyonel diyabet, diyabet komplikasyonları, gebelik komplikasyonları

Address for Correspondence: Akif Bayyiğit, University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
Phone: +90 532 747 29 70 E-mail: akif.bayyigit@gmail.com ORCID ID: orcid.org/0000-0002-9963-4809

Cite as: Tan S, Bayyiğit A. What is Gestational Diabetes Mellitus Awareness in Pregnant Women: A Survey Study. Med J Bakirkoy 2024;20:129-135

Received: 02.03.2024
Accepted: 10.06.2024

INTRODUCTION

Insulin resistance and pancreatic beta cell dysfunction during pregnancy negatively affect maternal and fetal health. A total of 9-25% of pregnancies worldwide are affected by acute or long-term complications (1).

According to the data in the Diabetes Atlas published by the International Diabetes Federation in 2021, 16.7% of 126.4 million women who were aged 20-49 who gave birth had diabetes. Among these, 80.3% had gestational diabetes mellitus (GDM), 9.1% had other types of diabetes and were diagnosed first during pregnancy, and the remaining 10.6% had pre-gestational diabetes mellitus (PGDM) (2).

During pregnancy, behaviors such as adopting healthy lifestyle behaviors, nutrition, diet, exercise, coping with stress, and taking health responsibility by self-monitoring blood glucose are effective in preventing GDM complications. Awareness among women about GDM and its risks to the fetus has effects on compliance with recommendations (3).

METHODS

Conducting the Study

This study was planned with a prospective survey design. The study was initiated with the approval of the University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee dated 08.08.2022 and decision numbered 236.

The patients who applied to the Internal Diseases and Gynecology and Obstetrics Outpatient Clinics of University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, were older than 18 years of age, passed the 24th gestational week, were diagnosed with GDM by applying a single or two-stage oral glucose tolerance test (OGTT), or had PGDM, and after the 24th gestational week, with known GDM and Pregestational DM between August 5, 2022 and September 15, 2022 were evaluated prospectively by obtaining the consent of the patients. A questionnaire was administered to the patients during their application for outpatient follow-ups. Informed consent was obtained by giving information beforehand, and education level, demographic characteristics, and knowledge level were investigated. The study had a cohort design with 300 patients, 250 of whom had no history of GDM and PGDM before 24 weeks of gestation, and 50 pregnant patients who had GDM and PGDM after 24 weeks of gestation. The sociodemographic characteristics of the patients were questioned, and a 20-item questionnaire was used to assess their awareness of GDM symptoms, general information about follow-up treatment, approach to OGTT, and fetal-maternal risks.

Data Collection Tool

A questionnaire was used as the data collection tool, the first part of which included sociodemographic characteristics such as age, height, body mass index (BMI), smoking, income level, and educational status, and the second part consisted of 20 items in total. One question included the approach to OGTT, two questions about GDM symptoms, two questions about blood glucose targets, three questions approach to treatments, eight questions about GDM complications, and one question about GDM information resources. The answers to questions 1 to 18 consisted of two options: "True" and "False". Item 19 consisted of seven options questioning the sources of information about GDM. In item 20, it was questioned whether pregnant women without pregestational DM, who were not diagnosed with GDM, and who were before the 24th gestational week were considering OGTT. The group with known pregestational DM and GDM was not asked this question. The questionnaire was adapted from similar studies (4-6).

The correct answers to questions 2, 4, 5, 6, 7, 11, 12, 15, and 17 were "True", and the correct answers to questions 1, 3, 8, 9, 10, 13, 14, 16, and 18 were "False". Awareness levels were determined by dividing the number of correctly answered questions by the number of answers.

When the tables were created, pregnant women with GDM and PGDM after 24 weeks of gestation were considered to have GDM (+), and pregnant women without known GDM before 24 weeks of gestation were considered as GDM (-).

Implementation and Evaluation of the Survey

The patients who met the inclusion criteria to participate in the survey were informed about the study, and the volunteers filled out the questionnaires through face-to-face interviews.

Statistical Analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In the evaluation of the data, as well as the descriptive statistical methods (mean, standard deviation, median, minimum, maximum), the distribution of the variables was examined with the Shapiro-Wilk normality test, the One-Way Analysis of Variance was used in the comparison of the normally distributed variables, the Tukey multiple comparison test was used in the subgroup comparisons, the independent t-test was used for the pairwise comparisons, and the chi-square test was used in the comparison of qualitative data. The results were evaluated at a significance level of $p<0.05$.

RESULTS

A total of 300 patients aged between 18 and 47 years with a mean age of 30.19±5.71 years participated in the study. The sociodemographic characteristics of the patients are listed in Table 1. The education level distributions were as follows; those who were literate were 35 participants (11.67%), 98 (32.67%) participants were primary school graduates, 90 (30%) were high school graduates, and 77 (25.67%) were university graduates. Regarding the distribution of income levels, the group earning less than 4253 Turkish Liras (TL) (the minimum wage at the time of study) constituted the majority (34%). Also, the group earning between 4254 and 5000 TL was 19%, and the group earning >7000 TL was 15%.

The detailed results of the GDM and its complication awareness questionnaire are given in Table 2.

Although the level of awareness was found to be higher in the groups with higher education and income status (Tables 3, 4), no significant differences were detected between the knowledge levels in the GDM (+) group and the GDM (-) group.

DISCUSSION

Although there is a good level of awareness regarding GDM and its complications in pregnant women, whether or not they have GDM, there is a lack of knowledge on some issues. The present study is among the first in our country to raise awareness of GDM and its complications, which are common in our country and are increasing in parallel with the obesity epidemic all over the world. The number of studies conducted on this subject is limited worldwide.

Table 1. Sociodemographic characteristics of the patients

		Entire patient group		GDM (-)		GDM (+)		p-value
Age (years)		30.19±5.71		29.87±5.78		31.08±5.11		0.169*
Age (years)	<35 Years	223	74.33%	189	75.60%	34	68.00%	0.261+
	≥35 Years	77	25.67%	61	24.40%	16	32.00%	
BMI (kg/m²)		27.45±5.04		26.54±4.46		31.99±5.37		**0.0001***
BMI (kg/m²)	<30 BMI	214	71.33%	194	77.60%	20	40.00%	**0.0001+**
	≥30 BMI	86	28.67%	56	22.40%	30	60.00%	
Number of pregnancies		2.51±1.54		2.35±1.44		3.28±1.79		**0.0001***
Number of children		1.27±1.2		1.2±1.14		1.64±1.38		**0.017***
Family history of DM		114	38.00%	85	34.00%	29	58.00%	**0.001+**
Education level	Literate	35	11.67%	26	10.40%	9	18.00%	0.337+
	Primary school	98	32.67%	81	32.40%	17	34.00%	
	High school	90	30.00%	79	31.60%	11	22.00%	
	University	77	25.67%	64	25.60%	13	26.00%	
Smoking		36	12.00%	33	13.20%	3	6.00%	0.153+
Income level	<4253 TL	102	34.00%	80	32.00%	22	44.00%	0.281+
	4254-5000 TL	57	19.00%	48	19.20%	9	18.00%	
	5001-7000 TL	96	32.00%	81	32.40%	15	30.00%	
	>7000 TL	45	15.00%	41	16.40%	4	8.00%	
Information sources	Internal medicine specialist	114	38.00%	69	27.60%	45	90.00%	**0.0001+**
	Family doctor	67	22.33%	61	24.40%	6	12.00%	0.055+
	Family and friends	24	8.00%	23	9.20%	1	2.00%	0.087+
	TV. newspapers	14	4.67%	12	4.80%	2	4.00%	0.807+
	Social media and the ınternet	56	18.67%	48	19.20%	8	16.00%	0.596+
	Pregnancy training school	11	3.67%	9	3.60%	2	4.00%	0.891+
	Other	38	12.67%	33	13.20%	5	10.00%	0.535+

*Independent t-test, +chi-square test, GDM (+): Pregnant women over 24 weeks of gestation with GDM and PGDM, GDM (-): Pregnant women without known diabetes before the 24th gestational week
GDM: Gestational diabetes mellitus, PGDM: Pre-gestational diabetes mellitus, BMI: Body mass index, TL: Turkish liras

Diabetes is a risk factor for the mother and fetus because of the degree of hyperglycemia and its chronic complications and related comorbidities (3,7). OGTT is recommended for pregnant women who have not been diagnosed with diabetes in the previous stages of pregnancy between weeks 24 and 28. Misconceptions and prejudices about OGTT reduce the participation of pregnant women in these tests that are used for diagnosis, and in case of missed diagnoses, both maternal and fetal risks increase and cause problems for generations that may result in the future development of type 2 DM, hypertension, and obesity in the child to be born. Although GDM is followed with a dynamic and variable treatment protocol, optimal follow-up can be achieved with the cooperation of the patient and clinician because it requires high patient compliance, adherence to diet, exercise, and self-monitoring of glucose at home, in addition to pharmacological treatment. The consciousness of patients is a factor that increases their adaptation (8).

Table 2. Detailed results of the GDM and complication awareness questionnaire

Number of correct answers and rates	Entire patient group		GDM (-)		GDM (+)		p-value[+]
GDM does not cause the baby to have an excessive birth weight.	179	65.57%	147	65.63%	32	65.31%	0.966
GDM increases the risk of shoulder dystocia.	145	57.77%	117	57.35%	28	59.57%	0.781
GDM does not increase the risk of neonatal jaundice.	166	64.59%	136	64.15%	30	66.67%	0.749
GDM increases the risk of stillbirth.	209	79.47%	169	78.60%	40	83.33%	0.463
GDM increases the risk of preterm birth.	232	87.88%	191	87.21%	41	91.11%	0.466
GDM increases the fluid that the baby is in the womb.	168	67.47%	141	68.78%	27	61.36%	0.341
GDM increases the risk of preeclampsia.	195	78.00%	168	81.16%	27	62.79%	**0.008**
Patients with GDM do not have an increased risk of developing DM after delivery.	152	59.61%	123	58.85%	29	63.04%	0.600
The oral glucose tolerance test can have negative consequences for pregnancy and the baby.	139	53.26%	113	52.56%	26	56.52%	0.625
Consuming too much sugar is a cause of diabetes.	54	20.45%	44	20.28%	10	21.28%	0.878
One hundred and fifty is a high value for fasting glucose during pregnancy.	205	80.71%	163	77.99%	42	93.33%	**0.018**
Two hundred is a high value for postprandial glucose in pregnancy.	191	79.25%	150	76.53%	41	91.11%	0.300
Medication is more important than diet for the control of diabetes during pregnancy.	157	63.56%	124	61.39%	33	73.33%	0.132
Shivering and sweating are signs of high blood glucose levels.	72	28.13%	49	23.22%	23	51.11%	**0.0001**
Excessive thirst and urination are signs of high blood glucose.	209	83.60%	168	82.35%	41	89.13%	0.262
The use of insulin leads to addiction.	138	56.56%	114	57.00%	24	54.55%	0.766
Postprandial blood glucose is measured 1 h after a meal in pregnant women.	212	87.60%	166	85.13%	46	97.87%	**0.017**
Walking and exercise have no effect on blood sugar regulation.	197	78.49%	166	80.98%	31	67.39%	**0.043**

[+]Chi-square test GDM (+): Pregnant women with GDM and PGDM past the 24th gestational week, GDM (-): Pregnant women without known diabetes before the 24th gestational week
GDM: Gestational diabetes mellitus PGDM: Pre-gestational diabetes mellitus

Table 3. Awareness comparison between the education level groups in the non-diabetic patient group

Tukey's multiple comparison test	Awareness level[*]
Literate/primary education	0.999
Literate/high school	0.510
Literate/university	**0.041**
Elementary/high school	0.100
Elementary/university	**0.001**
High school/university	0.386

[*]P-value

Table 4. Comparison of income distribution and awareness level of the non-diabetic patient group

Tukey's multiple comparison test	Awareness level[*]
<4253 TL/4254-5000 TL	0.951
<4253 TL/5001-7000 TL	**0.027**
<4253 TL/>7000 TL	**0.0001**
4254-5000 TL/5001-7000 TL	0.237
4254-5000 TL/>7000 TL	**0.007**
5001-7000 TL/>7000 TL	0.282

*P-value, TL: Turkish Liras

The prevalence of obesity in Türkiye was found to be 32% in TURDEP II (Turkish Diabetes Epidemiology Study), which is one of the most comprehensive studies conducted in Türkiye in which diabetes was evaluated epidemiologically, and it was found to be 28.6% in those who participated in this study.

Unlike the literature data, no age difference was detected between the group with GDM and PGDM and the group without diabetes; however, the mean age was found to be higher in the group with GDM and PGDM, and the rate of pregnant women aged 35 and over was higher in accordance with the literature data (9). The reason for the lack of difference might be that the non-diabetic group was born before the 24th gestational week and OGTT had not been performed. It is possible that some women were diagnosed with GDM in the following weeks of pregnancy.

Consistent with the literature data, the BMI values of the pregnant women who had GDM and PGDM were found to be significantly higher than those of pregnant women without diabetes, and the number of obese patients (BMI >30) in this group was significantly higher than that in the group without diabetes (p=0.0001) (10). Also, in accordance with the literature data, the incidence of DM in the family was significantly higher in the group with GDM and PGDM (p=0.001). The data of the TURGEP Study, which evaluated the prevalence and predictive factors of national GDM as one of the largest studies conducted in our country in 2019, were similar (9).

Gravida and parity ratios were high in the GDM and PGDM (p<0.05). In the study conducted by Gürkan et al. (11), an increased risk of GDM was found in the group with multiparity, especially in the group with four or more pregnancies.

The low rate of pregnant smokers (12%) can be interpreted as the risks of smoking during pregnancy were widely known with the policies implemented by the Ministry of Health.

Among all participants, the rate of patients who thought that insulin could be addictive was 43%, and 45.5% in the group with gestational diabetes and pregestational diabetes, who may need insulin during their follow-up. This was an important finding because it shows that a significant number of patients were biased toward insulin use and might resist initiating insulin, which is a reliable treatment option that has been used in pregnancy for many years in the face of necessary indications.

The fact that approximately one-third of the pregnant women who have GDM do not know that they have an increased risk of diabetes in later life, with their prevalence of type 2 DM being 38% in the first year and 60% in the next 16 years, will cause them to skip their follow-ups in this regard after delivery, they might have delayed diagnoses, and there will be an increase in the risk of complications (12,13).

Hypoglycemia, which can be life-threatening and cause serious complications if it persists for a long time, is important during pregnancy. It was noteworthy that only 20.45% of the participants knew that sweating and shivering were symptoms of hypoglycemia. Although this question had a higher rate of correct answers among diabetic pregnancies, it is serious that approximately half of them did not know the answer. Self-monitoring of blood glucose at home has great importance for patients with GDM. The fact that they do not know that sweating and shivering will be because of hypoglycemia will complicate the situations in which they can intervene on their own at home, and this will cause the patients who use insulin to lose their compliance with the treatment and even to stop their treatment.

GDM and PGDM pregnant women gave correct answers at an average rate of 66.2% to the questions in the survey of Quaresima et al. (14) on macrosomia, polyhydramnios, shoulder dystocia, preeclampsia, and fetal death risk associated with GDM complications. The correct answer rate was 51.8% in the GDM group in the study conducted by Quaresima et al. (14). This showed that the level of knowledge was higher in patients followed up in our center. More correct answers were given to the questions including information about fasting glucose value, blood glucose monitoring, and hypoglycemia symptoms in the group with GDM and PGDM compared with the non-diabetic group by over 90% of pregnant women. This result can be considered the success of the GDM outpatient clinics in our hospital. In a study by Hassan et al. (15) with 482 pregnant women, 65.6% answered the questions correctly, which is consistent

Table 5. Comparison of the tendency to have OGTT and the rate of correct answers to question 9

		Do you have the intent to have an OGTT?				
	No		**Yes**		**p-value**	
The oral glucose tolerance test can have negative outcomes for pregnancy and the baby.	Wrong answers	59	58.42%	40	39.60%	**0.006**
	Correct answers	42	41.58%	62	61.39%	

OGTT: Oral glucose tolerance test

with our findings. Similar results were obtained in a study by Ludowici (4) with 202 women aged 12-51 years.

It was found that a significant proportion of pregnant women considered that OGTT could be harmful to pregnancy and the fetus (46.7%). In the question on the pregnancy process and whether OGTT would harm the fetus, which was asked to pregnant women before the 24th gestational week who were not diagnosed with diabetes, pregnant women who considered it harmful remained significantly abstained from having OGTT (p=0.006) (Table 5). Similarly, in the study conducted by Dalgıç et al. (16), it was shown that 53% of pregnant women did not have OGTT because they considered it harmful and received information from the media that it was harmful. This shows that misinformation and prejudices are high because of information pollution and that more information should be given on this issue.

The information sources for GDM were mostly internal medicine specialists (38%), family physicians (22%), and social media and the internet. Similarly, the most common source of information about GDM was answered by doctors in the study by Price et al. (5) (30%). The fact that patients with GDM and PGDM were followed up in the internal diseases outpatient clinic was effective in increasing the rate of this response.

The general awareness level was found to be 65% in this study. The awareness level was found to be as high as 73% in the GDM awareness study conducted by Amr et al. (6) on women of reproductive age in the Sharjah region.

Although the level of awareness increased with increased education and income levels among pregnant women without diabetes, this difference between pregnant women with GDM and PGDM was closed with the knowledge of the subject after the diagnosis of pregnant women with low education and income levels, and no significant differences were detected according to income and education levels, and it was higher in pregnant women with obesity in this group.

When the factors that affected the awareness levels of the patients were evaluated, factors such as high education levels, high income levels, and smoking levels increased the awareness of GDM among the participants.

The fact that the awareness levels of smokers were high might be associated with the higher income levels and educational status of these people and the concern that smoking will harm the fetus with a greater risk. In the study conducted by Quaresima et al. (14), it was reported that the level of knowledge increased with the increased education levels. Although awareness was found to be higher in pregnant women with GDM and PGDM in the study, no difference was detected in terms of knowledge levels in pregnant women without diabetes. This result can be explained by the fact that the percentage of patients who had primary education and below level was 43% in the non-diabetic group and 52% in the group with GDM and PGDM, and education and awareness did not increase sufficiently in the diagnosed patients.

The fact that the present study was conducted in a single center may not reflect the same result as the entire society because it may have been conducted on similar groups in terms of sociodemographic, cultural, and educational levels. Conducting the study with larger patient groups might provide more statistically significant results.

CONCLUSION

GDM, which is predicted to be an important public healthcare concern in the coming years, can be controlled to a large extent by raising the awareness of pregnant women. This study demonstrated the need for more information and training. It is necessary to raise awareness of GDM and its complications and to raise the awareness of pregnant women about OGTT.

ETHICS

Ethics Committee Approval: The study was initiated with the approval of the University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee dated 08.08.2022 and decision numbered 236.

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

Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: S.T., Analysis or Interpretation: S.T., Literature Search: S.T., Writing: S.T., A.B.

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

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

REFERENCES

1. Alejandro EU, Mamerto TP, Chung G, Villavieja A, Gaus NL, Morgan E, et al. Gestational diabetes mellitus: A harbinger of the vicious cycle of diabetes. Int J Mol Sci 2020;21:5003.
2. Satman İ, İmamoğlu Ş, Yılmaz C, Ayvaz G, Çömlekçi A. Türkiye'de ve Dünya'da Diyabet. Türkiye Endokrinoloji Ve Metabolizma Derneği (TEMD) Diabetes Mellitus Çalışma ve Eğitim Grubu Raporu. Turkish Journal of Endocrinology and Metabolism 2012;16(Supplement 1).

3. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: A Study of Discordant Sibships. Diabetes. 2000;49:2208-11.
4. Ludowici E. Assessing Knowledge on Gestational Diabetes Mellitus and Child Health. Hawaii J Health Soc Welf 2023;82:227-31.
5. Price LA, Lock LJ, Archer LE, Ahmed Z. Awareness of Gestational Diabetes and its Risk Factors among Pregnant Women in Samoa. Hawaii J Med Public Health 2017;76:48-54.
6. Amr E, Batool AH, Rawan A, Amina B, Samher N. Gestational diabetes awareness in women of childbearing age in Sharjah. Glob J Obes Diabetes Metab Syndr 2017;4:51-3.
7. American Diabetes Association Professional Practice Committee. 15. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2022. Diabetes Care 2022;45(Suppl 1):S232-S43.
8. Trutnovsky G, Panzitt T, Magnet E, Stern C, Lang U, Dorfer M. Gestational diabetes: Women's concerns, mood state, quality of life and treatment satisfaction. J Matern Fetal Neonatal Med 2012;25:2464-6.
9. Aydın H, Çelik Ö, Yazıcı D, Altunok Ç, Tarçın Ö, Deyneli O, et al. Prevalence and predictors of gestational diabetes mellitus: a nationwide multicentre prospective study. Diabet Med 2019;36:221-7.
10. TEMD Diabetes Mellitus Çalışma ve Eğitim Grubu. Diabetes Mellitus ve Komplikasyonlarının Tanı, Tedavi ve İzlem Kılavuzu. 2022.
11. Gürkan E, Dirican E, Bülbül N. The Effect of Common and Possible Risk Factors' Co-occurrence to the Development of Gestational Diabetes Mellitus. Ankara Medical Journal 2018;18:382-90.
12. Metzger BE, Bybee DE, Freinkel N, Phelps RL, Radvany RM, Vaisrub N. Gestational diabetes mellitus. Correlations between the phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during the first year postpartum. Diabetes 1985;34 Suppl 2:111-5.
13. O'Dea A, Tierney M, McGuire BE, Newell J, Glynn LG, Gibson I, et al. Can the onset of type 2 diabetes be delayed by a group-based lifestyle intervention in women with prediabetes following gestational diabetes mellitus (GDM)? Findings from a randomized control mixed methods trial. J Diabetes Res 2015;2015:798460.
14. Quaresima P, Visconti F, Interlandi F, Puccio L, Caroleo P, Amendola G, et al. Awareness of gestational diabetes mellitus foetal-maternal risks: an Italian cohort study on pregnant women. BMC Pregnancy Childbirth 2021;21:692.
15. Hassan AM, Alghamdi GS, Alfantoukh AM, Aljohani A, Alzahrani FA, Eissa GA, et al. Evaluation of Knowledge About Gestational Diabetes Among Primigravidae Versus Multigravidae in Saudi Arabia: A Quantitative Cross-Sectional Study. Cureus 2023;15:e50458.
16. Dalgıç N, Aşık Z, Özen M. Evaluation of approaches of gestational diabetes screening test in pregnant women. Jour Turk Fam Phy 2020;11:179-90.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:136-141
DOI: 10.4274/BMJ.galenos.2023.2023.10-10

Research

Culture-proven Bacterial Conjunctivitis in Newborns: Five-year Single-center Experience

Kültür Kanıtlı Yenidoğan Bakteriyel Konjonktiviteleri: 5 Yıllık Tek Merkez Deneyimi

Salih Demirhan[1], Hacer Aktürk[2], Gökhan Çelik[3], Sevilay Topçuoğlu[4], Funda Erdek[5], Güner Karatekin[4]

[1]University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital, Clinic of Pediatrics, İstanbul, Türkiye
[2]Koç University Hospital, Department of Pediatrics, Division of Infectious Diseases, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital, Clinic of Pediatrics, Divison of Neonatology, İstanbul, Türkiye
[5]University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital, Pediatric Infection Control Committee, İstanbul, Türkiye

ABSTRACT

Objective: The data on neonatal conjunctivitis are significantly limited in Türkiye. In this study, we aimed to investigate the epidemiology of neonatal bacterial conjunctivitis and the clinical and laboratory findings of patients in a tertiary neonatal referral hospital in İstanbul, Türkiye.

Methods: This retrospective observational study was conducted over a five-year period between January 2015 and January 2020. Newborns 28 days of age who presented to our clinics with clinical features of conjunctivitis and had bacterial growth in the conjunctival culture were included.

Results: Thirty-two newborns with culture-proven bacterial conjunctivitis were included. A total of 26 (81.3%) newborns required newborn intensive care unit (NICU) admission. Gram-positive bacteria growth was detected in 47% (n=15) of cases, and gram-negative growth was detected in 53% (n=17) of cases. *Escherichia coli* (n=12), *Staphylococcus epidermidis* (n=10) and *Staphylococcus aureus* (n=3) were the most frequently identified bacteria. The proportions of newborns with need for intravenous (IV) antibiotic treatment, bilateral eye involvement, and normal spontaneous delivery were significantly higher in the gram-negative conjunctivitis group.

Conclusion: Our study provides important data regarding bacterial conjunctivitis in newborns in Türkiye, given that data in Türkiye are very limited. The high rates of NICUs admission, presence of clinical sepsis, and IV antibiotic administration show the importance of neonatal conjunctivitis as a clinical finding of systemic neonatal infections. Despite the lack of universal ocular prophylaxis in our high-volume neonatal referral center, the low number of culture-proven conjunctivitis cases challenges the current routine ocular prophylaxis suggestions.

Keywords: Conjunctivitis, ophthalmia neonatorum, newborn

ÖZ

Amaç: Türkiye'de yenidoğan konjonktiviti ile ilgili veriler oldukça sınırlıdır. Bu çalışmada İstanbul'da üçüncü basamak bir yenidoğan refereans merkezindeki neonatal bakteriyel konjonktivit epidemiyolojisini ve hastaların klinik ve laboratuvar bulgularını araştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif gözlemsel çalışma, Ocak 2015 ile Ocak 2020 arasındaki beş yıllık dönemde gerçekleştirildi. Kliniğimize konjonktivit semptomları ile başvuran ve konjonktival kültüründe bakteri üremesi olan, 28 günlükten küçük yenidoğanlar çalışmaya dahil edildi.

Bulgular: Kültürle kanıtlanmış bakteriyel konjonktiviti olan 32 yenidoğan çalışmaya dahil edildi ve 26'sının (%81,3) yenidoğan yoğun bakım ünitesinde (YYBÜ) takibi yapıldı. Olguların %47'sinde (n=15) gram-pozitif bakteri üremesi, olguların %53'ünde (n=17) gram-negatif üreme saptandı. *Escherichia coli* (n=12), *Staphylococcus epidermidis* (n=10) ve *Staphylococcus aureus* (n=3) en sık tespit edilen bakterilerdi.

Address for Correspondence: Salih Demirhan, The Children's Hospital at Montefiore - The Pediatric Hospital for Albert Einstein College of Medicine, Division of Pediatric Infectious Diseases, New York, USA
Phone: +1 718-741-2470 E-mail: ssalihdemirhan@gmail.com ORCID ID: orcid.org/0000-0001-5476-0353

Cite as: Demirhan S, Aktürk H, Çelik G, Topçuoğlu S, Erdek F, Karatekin G. Culture-proven Bacterial Conjunctivitis in Newborns: Five-year Single-center Experience. Med J Bakirkoy 2024;20:136-141

Presented in: Preliminary findings of this study were presented at 3rd Young Paediatricians Congress, İstanbul, Türkiye.

Received: 07.11.2023
Accepted: 12.12.2023

ÖZ

Gram-negatif konjonktivit grubunda intravenöz (İV) antibiyotik tedavisi gerektiren, iki taraflı göz tutulumu olan ve normal spontan doğum ile doğan yenidoğan oranları anlamlı olarak daha yüksekti.

Sonuç: Çalışmamız verilerin oldukça sınırlı olduğu ülkemizde yenidoğanlarda bakteriyel konjonktivit ile ilgili önemli bulgular sunmaktadır. YYBÜ takibi ve İV antibiyotik gerektiren ve sepsis klinik bulguları olan yenidoğanların oranlarının yüksek olması, sistemik yenidoğan enfeksiyonlarının klinik bulgusu olarak yenidoğan konjonktivitinin önemini göstermektedir. Rutin oküler profilaksi uygulanmayan referans merkezimizdeki 5 yıllık süre zarfında kültürle kanıtlanmış konjonktivit olgularının az sayıda olması, mevcut rutin oküler profilaksi önerilerinin tekrar değerlendirilmesi gerektiği konusunda fikir vermektedir.

Anahtar Kelimeler: Konjonktivit, oftalmia neonatorum, yenidoğan

INTRODUCTION

Conjunctivitis, which is seen in the first month of life, is called ophthalmia neonatorum (ON). The ON incidence ranges from 1.6% to 12% (1). The most important cause of neonatal blindness globally was neonatal conjunctivitis before the twentieth century (2). Keratitis, dacryocystitis, nasolacrimal duct obstruction, cellulitis, and glaucoma are the differential diagnoses of neonatal conjunctivitis; and it has serious complications such as corneal ulcers, eye perforation, blindness, systemic spread; sepsis, meningitis, and pneumonia if left untreated (3). Although the clinical features of neonatal conjunctivitis, such as conjunctival erythema, edema, and discharge, are similar to those of conjunctivitis in older individuals, it is a medical condition that should be diagnosed and treated urgently in newborns, considering the possible disease progression and systemic infections that may accompany it.

The silver nitrate 2% prophylaxis recommended by Dr. Crede in 1881 was a turning point in ON (4). The rate of *Neisseria gonorrhoeae* infection in ON cases decreased from 10% to 0.3% in the post-prophylaxis period (5). Better prophylaxis options were tried because of chemical conjunctivitis, the common side effects of silver nitrate; and different antibiotic ointments and diluted povidone-iodine solutions have been used in ON prophylaxis. Today, there is still no clear consensus on ON prophylaxis, and each country and society has different suggestions regarding the role and method of universal ocular prophylaxis (6).

Although bacterial agents cause most conjunctivitis cases in the neonatal period, viral and chemical conjunctivitis are also observed in the neonatal period. Classically, the causative agents of bacterial conjunctivitis are *Chlamydia trachomatis* and *N. gonorrhoeae*, whereas gram-positive bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and viridans *Streptococci*; and gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, and other gram-negative enteric bacteria are known to cause bacterial conjunctivitis (7).

The data on neonatal conjunctivitis are significantly limited in Türkiye. In this study, we aimed to investigate the epidemiology of neonatal bacterial conjunctivitis and the clinical and laboratory findings of patients in a tertiary neonatal referral hospital in İstanbul, Türkiye.

METHODS

Ethics

Our single-center study was retrospectively designed over a 5-year period between January 2015 and January 2020. Study approval was obtained from the University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee (decision no: 16, date: 20.01.2021). Consent was waived because of the retrospective nature of the study.

Study Population and Inclusion Criteria

Demographic and clinical characteristics, such as birth weight, gestational age, mode of delivery, postnatal age, maternal data, and laboratory data, were obtained from electronic medical records. Newborns 28 days of age who presented to our clinics with clinical features of conjunctivitis and had bacterial growth in the conjunctival culture were included in our study. Only community-acquired conjunctivitis cases were included. Hospital-acquired conjunctivitis cases based on the Centers for Disease Control and Prevention guidelines were excluded (8).

Study Setting and Conjunctivitis Diagnosis

A total of 39,138 babies were delivered in our tertiary referral center over 5 years. An average of 1500 newborns were admitted to our neonatal intensive care unit (NICU) annually. Eyecare with normal saline and gauze is routinely performed for babies born in our hospital, but conjunctivitis prophylaxis is not administered. Newborns are discharged from the newborn nursery at least 24 h after normal spontaneous delivery (NSD) and 48 h after cesarean section. Conjunctival cultures were obtained from newborns with clinical findings of conjunctivitis in our hospital's outpatient clinics, nursery services, and NICUs. In preparation for culture, the

periorbital area was cleaned with sterile gauze and normal saline. Culture was taken from the lower conjunctiva using a cotton swab. Particular attention was paid to prevent touching eyelids and eyelashes while taking the culture. The sample taken on a cotton swab was transferred to a transport tube containing the medium. Culture inoculation, microbiological identification, and antibiotic susceptibility tests were performed in a microbiology laboratory. Management and follow-up were performed by attending pediatricians, neonatologists, or ophthalmologists. While topical antibiotic treatment was administered to all patients, intravenous (IV) antibiotic treatment and hospitalization were deemed necessary for some newborns when systemic infection was suspected.

Statistical Analysis

Statistical analysis was performed using Stata version 17.0 (Stata Corp LLC, College Station, Texas). The distribution of continuous variables was assessed using histograms and statistical methods. Continuous variables were presented as "mean ± standard deviation" or median [interquartile range (IQR) 25-75 percentile] according to the distribution normality; and categorical variables were presented as "number (percentage)". Patients were divided into two groups based on the bacteria causing conjunctivitis: gram-positive and gram-negative groups. Comparison of categorical variables between groups was made using the chi-square or Fisher's exact test. Comparison of continuous variables was performed using Student's t-test or Mann-Whitney U test if normality assumptions were not met. A $p<0.05$ level was set for statistical significance.

RESULTS

Thirty-two newborns with clinical signs of conjunctivitis and bacterial growth on conjunctival cultures were included in our study during the 5-year study period. While 43.8% (n=14) of the patients were female, 56.2% (n=18) were male. The mean birth weight and gestational age were 3024±728 grams and 37.6±2.8 weeks, respectively (Table 1).

Unilateral involvement was noted in 56.3% of the patients (n=18), and 43.7% (n=14) had bilateral conjunctivitis. Conjunctival edema (chemosis) was detected in 21.9% patients. A total of 26 (81.3%) newborns required NICU admission, and the indication for NICU admission was conjunctivitis in 6 patients. Other indications for NICU admission were respiratory distress (n=11), prematurity (n=5), jaundice (n=3) and congenital malformation (n=1). Neonatal sepsis was clinically diagnosed in 14 patients. Only two of them had culture-proven sepsis, and both blood and conjunctival cultures grew the same bacteria. IV antibiotic treatment was initiated in 62.5% (n=7) of the patients for a median of 7 (IQR 6-10) days. High C-reactive protein (>1 mg/dL) was found in 18.7% (n=6) of the patients. The clinical and laboratory data of our cohort are shown in Table 2.

In conjunctival cultures, gram-positive bacteria growth was detected in 47% (n=15) of cases, and gram-negative growth was detected in 53% (n=17) of cases. *E. coli* (n=12), *S. epidermidis* (n=10) and *S. aureus* (n=3) were the most frequently identified bacteria in the study. The etiological distribution of the 32 neonatal conjunctivitis cases in our study is reported in Table 3.

The majority of neonatal conjunctivitis cases were diagnosed in spring (43.8%), followed by summer (37.5%), fall (6.2%), and winter (12.5%) months. There was a statistically significant seasonal difference between gram-positive and gram-negative conjunctivitis cases. All gram-negative conjunctivitis cases were diagnosed in spring and summer months, whereas 60% (n= 9) of gram-positive conjunctivitis

Table 1. Demographic features of newborns with culture-proven conjunctivitis

Demographic features	n=32
Gender, girl*	14 (43.8)
Birth weight, gram[1]	3024±782
Gestational age, week[1]	37.6±2.8
Mode of delivery, NSD*	18 (56.3)
Maternal age, year[1]	29.3±6.3
Oligohydramnios*	3 (9.4)
Premature rupture of membrane*	2 (6.3)

*n (%), [1]Mean ± standard deviation, NSD: Normal spontaneous delivery

Table 2. Clinical and laboratory findings of newborns with culture-proven conjunctivitis

Clinical findings	n=32
Unilateral eye involvement*	18 (56.3)
Conjunctival edema*	7 (21.9)
Clinical sepsis*	14 (43.8)
Culture-proven sepsis*	2 (6.3)
NICU admission*	26 (81.3)
Length of stay in NICU[2]	9 (2-60)
Intravenous antibiotic use*	20 (62.5)
Length of intravenous antibiotic use, day[2]	7 (6-10)
Laboratory findings	
Leucocyte x1000/μL[1]	14.7±5.7
Neutrophil x1000/μL[1]	8.5±4.7
Thrombocyte x1000/μL[1]	287±128
C-reactive protein, mg/dL[2]	0.2 (0.1-0.54)

*n (%), [1]Mean ± standard deviation, [2]Median (IQR), NICU: Newborn intensive care unit, IQR: Interquartile range

cases were detected in spring and summer months (p=0.01). The seasonal distribution of conjunctivitis cases is shown in Table 4.

Of the 32 neonatal conjunctivitis cases in our study, 25 (78.2%) were diagnosed in the first week of life, followed by 4 (12.5%) in the second week of life, 2 (6.2%) in the third week of life, and 1 (3%) in the fourth week of life. Gram-negative conjunctivitis cases were diagnosed earlier than gram-positive cases [1 (IQR 1-3) days vs. 6 (IQR 3-11) days, p=0.002] and all gram-negative conjunctivitis cases were diagnosed in the first week of life (Figure 1).

Newborns with gram-negative conjunctivitis had a significantly higher proportion of NSD delivery (76.5%) than those with gram-positive conjunctivitis (33.3%, p=0.01) Bilateral eye involvement was present in 26.7% (n= 4) of newborns with gram-positive conjunctivitis and 58.8% of newborns with gram-negative conjunctivitis. This difference between the groups was statistically significant (p=0.04). The need for IV antibiotics was higher in the gram-negative conjunctivitis group (p=0.01). Complete demographics and clinical characteristics comparison between the gram-negative and gram-positive groups are shown in Table 5.

Table 3. Etiology of culture-proven neonatal conjunctivitis

	n=32
Gram-positive*	**15 (47)**
*Staphylococcus epidermidis**	10 (31.2)
*Staphylococcus aureus**	3 (9.4)
*Streptococcus pneumoniae**	1 (3.1)
Corynebacterium spp.*	1 (3.1)
Gram-negative*	**17 (53)**
*Escherichia coli**	12 (37.5)
*Klebsiella pneumoniae**	2 (6.3)
*Enterobacter aerogenes**	1 (3.1)
*Pseudomonas aeruginosa**	1 (3.1)
*Neisseria gonorrhoeae**	1 (3.1)

*n (%)

Table 4. Seasonal distribution of conjunctivitis

Season	Overall n=32	Gram-positive n=15	Gram-negative n=17	p-value
Spring*	14 (43.8)	6 (40)	8 (47.1)	0.01
Summer*	12 (37.5)	3 (20)	9 (52.9)	
Fall*	2 (6.2)	2 (13.3)	0 (0)	
Winter*	4 (12.5)	4 (26.7)	0 (0)	

*n (%)

DISCUSSION

Although complications due to neonatal conjunctivitis have decreased considerably worldwide, it remains a significant cause of neonatal morbidity. Unfortunately, our data do not provide a reliable incidence rate because some patients might have been treated empirically without obtaining conjunctival culture. However, the fact that the total number of culture-proven conjunctivitis cases in 5 years was only 32 is an important clue regarding its incidence considering the significantly high volume of patients who have been delivered and seen in our referral center. In the setting of a low number of cases, we speculate that our approach of no eye chemoprophylaxis after delivery did not result in high numbers of neonatal conjunctivitis cases, although this remains to be proven in large prospective studies.

Classical neonatal conjunctivitis pathogens, *C. trachomatis* and *N. gonorrhea,* are sexually transmitted diseases (STD) and newborns acquire these bacteria during the perinatal period; and the lack of robust STD incidence in childbearing aged women is an important obstacle to understanding the burden of neonatal conjunctivitis and the need for universal prophylaxis in our country. The current recommendation by the Turkish Ministry of Health is universal conjunctivitis prophylaxis according to "Basic Newborn Care" book published by the General Directorate of Public Health (9). However, each clinic makes its own instructional decision. In a study including 48 hospitals in Türkiye, 42% of the hospitals did not routinely administer conjunctivitis prophylaxis; and there was no consensus regarding prophylaxis methods among hospitals applying routine prophylaxis (10). Seven different agents were administered in prophylaxis-applying hospitals (10). The debate over the utility of conjunctivitis prophylaxis is not unique to Türkiye. A study conducted by the American Pediatric Ophthalmology and Strabismus Society surveyed 291 members working in different countries and continents and found that conjunctivitis prophylaxis was not performed in 21% of survey participating hospitals (11).

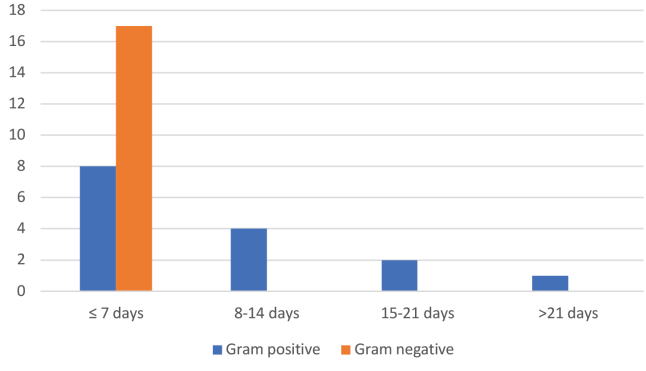

Figure 1. Postnatal age at the conjunctivitis diagnosis

Table 5. Comparison of patient data between gram-positive and gram-negative groups

	Gram-positive n=15	Gram-negative n=17	p-value
Gender, girl*	6 (40)	8 (47.1)	0.6
Birth weight, gram[1]	3095±841	3000±739	0.7
Gestational age, week[1]	37±2.7	38.2±2.6	0.1
Mode of delivery, NSD*	5 (33.3)	13 (76.5)	0.01
Maternal age, year[1]	31±6.6	27.5±5.7	0.1
Oligohydramnios*	0 (0)	3 (17.6)	0.2
Premature rupture of membrane*	0 (0)	2 (11.8)	0.4
Unilateral eye involvement*	11 (73.3)	7 (41.2)	0.04
Conjunctival edema*	3 (20)	4 (23.5)	1
Clinical sepsis*	5 (33.3)	9 (52.9)	0.2
Culture-proven sepsis*	1 (6.7)	1 (5.9)	1
NICU admission*	11 (73.3)	15 (88.2)	0.3
Length of stay in NICU[2]	7 (2-54)	9 (4-60)	0.9
IV antibiotic use*	6 (40)	14 (82.4)	0.01
Length of IV antibiotic use, day[2]	8 (7-10)	7 (6-10)	0.6
Leucocyte x1000/µL[1]	15.4±5.7	14.3±5.9	0.6
Neutrophil x1000/µL[1]	7±3.2	9.4±5.3	0.2
Thrombocyte x1000/µL[1]	334±149	257±107	0.1
C-reactive protein, mg/dL[2]	0.2 (0.2-0.4)	0.2 (0.2-1.2)	0.9

*n (%), [1]Mean ± standard deviation, [2]median (IQR), NSD: Normal spontaneous delivery, NICU: Newborn intensive care unit, IV: Intravenous, IQR: Interquartile range

Although the estimated rate of neonatal conjunctivitis due to *N. gonorrhea* in the United States is less than 1 case per 100,000 livebirth, the United States Preventative Service Task Force still recommends universal prophylaxis because of high perinatal transmission rates without ocular prophylaxis and significant morbidity related to gonococcal conjunctivitis (12).

The absence of erythromycin's prophylactic effect against *C. trachomatis* infections (13) and lack of literature support for universal ocular prophylaxis have raised questions about the necessity of universal ocular prophylaxis (14). Selecting antibiotic-resistant pathogens is another concern regarding routine antibiotic prophylaxis, and some experts suggest using a 2.5% povidone-iodine solution rather than antibiotic ointments for prophylaxis because of the increasing antibiotic resistance in neonatal conjunctivitis (15). Implementing strong maternal STD screening and treatment programs would further decrease the need for universal prophylaxis in our country and globally (16).

Although most of the clinical and laboratory findings were similar between gram-negative and gram-positive conjunctivitis cases, there were also remarkable differences. Newborns with gram-negative conjunctivitis were diagnosed earlier and had a more severe disease course (bilateral eye involvement, need for IV antibiotics) than gram-positive cases. The higher proportion of NSD in the gram-negative group than in the gram-positive group likely reflects the acquisition of causative pathogens from maternal genitourinary flora during passage through the birth canal (17). Similar to previous studies, our study detected conjunctivitis cases most commonly in the spring and summer (18). This seasonal difference was more prominent in gram-negative conjunctivitis cases in this study.

S. epidermidis was one of the most common etiologies of bacterial neonatal conjunctivitis in our study. The importance of coagulase-negative *Staphylococci* growth in conjunctival culture is controversial. Historically, coagulase-negative *Staphylococci* have been accepted as contaminants in conjunctival cultures (19). However, more recent studies have considered *S. epidermidis* as a causative agent in conjunctivitis. In one systematic review, *S. epidermidis* was found to be the second most common bacterial ocular infection pathogen after *S. aureus* (19). There is also emerging evidence that *S. epidermidis* can cause inflammation and infection in the conjunctiva and eyes (19).

Although we had a low number of newborns with culture-proven bacterial conjunctivitis, the percentage of patients who needed conjunctivitis-related NICU admission and IV antibiotics was relatively high. Moreover, two patients had culture-proven sepsis with the same bacteria found in the conjunctival culture, and 43% of the newborns with

conjunctivitis had clinical sepsis. Our findings suggest that prompt diagnosis and treatment of neonatal conjunctivitis is crucial, and conjunctivitis can be an initial symptom of more severe systemic infection. Contrary to our results, only 3/52 patients (6%) received IV antibiotics in a recent study from Canada; however, only 5 patients had culture-proven neonatal conjunctivitis in their study (20).

The retrospective design and small cohort were the most important limitations of our study. Another important limitation was the lack of access to molecular diagnostic tests for *C. trachomatis*. Although the incidence of *C. trachomatis* positivity in women is low in Türkiye (19), it is still one of the most common causes of newborn conjunctivitis.

CONCLUSION

In conclusion, our study provides important data regarding bacterial conjunctivitis in newborns in Türkiye, given that data in Türkiye are very limited. The high rates of NICU admission, presence of clinical sepsis, and IV antibiotic administration show the importance of neonatal conjunctivitis as a clinical finding of systemic neonatal infections. Despite the lack of universal ocular prophylaxis in our high-volume neonatal referral center, the low number of culture-proven conjunctivitis cases challenges the current routine ocular prophylaxis suggestions. Only one patient had gonococcal conjunctivitis, which is a historical target of ocular prophylaxis. However, our results may not be generalizable because of their single-center nature. Prospective multicenter studies in Türkiye are needed to better answer the question of ocular chemoprophylaxis.

ETHICS

Ethics Committee Approval: Study approval was obtained from the University of Health Sciences Türkiye, Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee (decision no: 16, date: 20.01.2021).

Informed Consent: Consent was waived because of the retrospective nature of the study.

Authorship Contributions

Surgical and Medical Practices: S.D., H.A., G.Ç., S.T., G.K., Concept: S.D., H.A., Design: S.D., H.A., Data Collection or Processing: S.D., H.A., G.Ç., S.T., F.E., Analysis or Interpretation: S.D., Literature Search: S.D., Writing: S.D.

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

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

REFERENCES

1. Wagner RS, Aquino M. Pediatric ocular inflammation. Immunol Allergy Clin North Am 2008;28:169-88.
2. Teoh DL, Reynolds S. Diagnosis and management of pediatric conjunctivitis. Pediatr Emerg Care 2003;19:48-55.
3. Makker K, Nassar GN, Kaufman EJ. Neonatal Conjunctivitis. 2023 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
4. Castro Ochoa KJ, Mendez MD. Ophthalmia Neonatorum. 2023 Jan 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
5. Matejcek A, Goldman RD. Treatment and prevention of ophthalmia neonatorum. Can Fam Physician 2013;59:1187-90.
6. Celik M, Altun Köroğlu Ö. Ocular prophylaxis in the newborn. Eur Eye Res 2022;2:80-3.
7. Hosal MB. Yenidoğan Konjonktiviti. Turkiye Klinikleri J Ophthalmol-Special Topics 2012;5:37-40.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309-32.
9. Temel Yenidoğan Bakımı. Ankara: T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü; 2017.
10. Eser İ. A nationwide survey of prophylaxis against ophthalmia neonatorum in Turkey. Turkish Journal of Medical Sciences 2009;39:771-4.
11. Zloto O, Gharaibeh A, Mezer E, Stankovic B, Isenberg S, Wygnanski-Jaffe T. Ophthalmia neonatorum treatment and prophylaxis: IPOSC global study. Graefes Arch Clin Exp Ophthalmol 2016;254:577-82.
12. Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Ocular Prophylaxis for Gonococcal Ophthalmia Neonatorum: US Preventive Services Task Force Reaffirmation Recommendation Statement. Jama 2019;321:394-8.
13. Smith-Norowitz TA, Ukaegbu C, Kohlhoff S, Hammerschlag MR. Neonatal prophylaxis with antibiotic containing ointments does not reduce incidence of chlamydial conjunctivitis in newborns. BMC Infect Dis 2021;21:270.
14. Franco S, Hammerschlag MR. Neonatal ocular prophylaxis in the United States: is it still necessary? Expert Rev Anti Infect Ther 2023;21:503-11.
15. Meyer D. Ophthalmia neonatorum prophylaxis and the 21st century antimicrobial resistance challenge. Middle East Afr J Ophthalmol 2014;21:203-4.
16. Auriti C, Mondì V, Aversa S, Merazzi D, Lozzi S, Petroni S, et al. OPHTHALMIA NEONATORUM in Italy: it is time for change. Italian Journal of Pediatrics 2021;47:238.
17. Amini E, Ghasemi M, Daneshjou K. A five-year study in Iran of ophthalmia neonatorum: prevalence and etiology. Med Sci Monit 2008;14:Cr90-6.
18. Di Bartolomeo S, Mirta DH, Janer M, Rodríguez Fermepin MR, Sauka D, Magariños F, et al. Incidence of Chlamydia trachomatis and other potential pathogens in neonatal conjunctivitis. Int J Infect Dis 2001;5:139-43.
19. Köse, Şükran, Ersan G, Sender SS, Devrim I, Inal MM. A prevalence study of Chlamydia infections in Turkish population. Braz J Infect Dis 2013;17:114-5.
20. St-Onge-St-Hilaire A, Boutin A, Gravel J. Is Ophthalmia Neonatorum Associated With Invasive Bacterial Infection? A Single-Center Retrospective Study. Pediatr Emerg Care 2023;39:858-62.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:142-151
DOI: 10.4274/BMJ.galenos.2024.2024.1-7

Research

Clinical Assessment of Children with Celiac Disease Compliant to Diet by Age

Diyete Uyum Sağlayan Çölyak Hastalığı Olan Çocukların Yaşa Göre Klinik Olarak Değerlendirmesi

Banu Özata Abanoz[1], Nafiye Urgancı[2], Merve Usta[2], Dilek Güller[2]

[1]University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatrics, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Gastroenterology, İstanbul, Türkiye

ABSTRACT

Objective: The aim of this study was to evaluate pediatric patients with celiac disease (CD) compliant with gluten-free diet (GFD) by age groups and determine the relationship between the duration of compliance with diet, anthropometric measurements, and laboratory parameters.

Methods: A total of 195 children with CD (mean age: 7.3±4.4, male/female: 0.69) who were compliant with GFD were enrolled in this retrospective study. Clinical and demographic characteristics, laboratory examinations, serological tests, histopathological findings, and genetic analysis of the patients were examined according to age groups at diagnosis, 6 months, and 1st and 2nd years of follow-up.

Results: 19.5% of the patients were ≤2 years old, and most of the patients were between 5 and 9 years of age. 68.2% of the patients were typical, 26.2% were atypical, and 5.6% were asymptomatic. The most common presenting symptoms were growth retardation, diarrhea, and abdominal distension in children ≤2 years of age. When the patients were classified according to height and weight standard deviation scores, no statistically significant differences were observed during follow-up (p>0.05). As the duration of compliance to GFD increased, the number of patients who were normal and overweight increased. Additionally, significant differences were observed in body mass index Z-scores among age groups during follow-up.

Conclusion: Growth retardation, diarrhea, and abdominal distension are the predominant symptoms in infants. As age increases, atypical presentation becomes more common. Longer the duration of compliance with GFD, improvement in anthropometric measurements and laboratory parameters are more prominent.

Keywords: Celiac disease, children, gluten-free diet, age group

ÖZ

Amaç: Çalışmanın amacı glutensiz diyete (GD) uyumlu çölyak hastalığı (ÇH) olan çocukları yaş gruplarına göre değerlendirmek ve diyete uyum süresi, antropometrik ölçümler ve laboratuvar parametreleri arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya, GD'yle uyumlu toplam 195 ÇH tanılı çocuk (ortalama yaş: 7,3±4,4, erkek/kız: 0,69) dahil edildi. Hastaların klinik ve demografik özellikleri, laboratuvar muayeneleri, serolojik testleri, histopatolojik bulguları ve genetik analizleri tanı anındaki yaş gruplarına, 6. ay, 1. ve 2. yıl takiplerine göre incelendi.

Bulgular: Hastaların %19,5'i ≤2 yaş grubunda olup, çoğunluğu 5-9 yaş aralığındaydı. Hastaların %68,2'si tipik, %26,2'si atipik ve %5,6'sı asemptomatikti. ≤2 yaş çocuklarda en sık görülen semptomlar büyüme geriliği, ishal ve karın şişliğiydi. Hastalar boy ve kilo standart sapma skorlarına göre sınıflandırıldığında takip sırasında istatistiksel olarak anlamlı farklılık elde edilmedi (p>0,05). GD'ye uyum süresi arttıkça normal ve aşırı kilolu hasta sayısı da arttı. Ayrıca takip sırasında yaş grupları arasında vücut kitle indeksi Z-skorlarında anlamlı farklılık gözlendi.

Sonuç: Büyüme geriliği, ishal ve karın şişliği bebeklerde halen en sık görülen semptomlardır. Yaş arttıkça atipik seyir daha sık görülür. GD'ye uyum süresi uzadıkça antropometrik ölçümlerde ve laboratuvar parametrelerinde iyileşme daha belirgindir.

Anahtar Kelimeler: Çölyak hastalığı, çocuklar, glutensiz diyet, yaş grubu

Address for Correspondence: Nafiye Urgancı, University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Gastroenterology, İstanbul, Türkiye
Phone: +90 212 338 63 00 E-mail: nafiyeurganci@yahoo.com ORCID ID: orcid.org/0000-0003-4854-507X

Cite as: Özata Abanoz B, Urgancı N, Usta M, Güller D. Clinical Assessment of Children with Celiac Disease Compliant to Diet by Age. Med J Bakirkoy 2024;20:142-151

Received: 25.01.2024
Accepted: 25.03.2024

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy induced by dietary gluten in genetically predisposed individuals and is characterized by abdominal distention, diarrhea, and growth retardation. CD can occur at any age and its prevalence is estimated to be 1% worldwide and varies depending on geographical and ethnic variations (1).

Environmental, immunological, and genetic factors play a role in the pathogenesis of the disease (2). Dietary gluten intake causes a natural and acquired immune response in the body, which leads to intestinal villi atrophy, crypt hyperplasia, and lymphocyte infiltration. Approximately 90-95% of the patients are human leukocyte antigen (HLA) DQ2 positive, whereas the rest are HLA-DQ8 positive (3).

The diagnosis of CD is based on serological tests and biopsy, the gold standard in diagnosis. CD is classified according to clinical findings as typical (classical), atypical, asymptomatic (silent), latent, or potential (2). Typical disease occurs in the first 6-24 months of life after dietary gluten intake begins and is characterized by growth retardation, gastrointestinal symptoms such as chronic diarrhea or watery stool, vomiting, abdominal pain, and distention. The atypical form is more common in older children and adults and is characterized by extraintestinal symptoms such as delayed puberty, short stature, iron deficiency anemia, and abnormal liver function.

The only effective treatment is a lifelong gluten-free diet (GFD). Children on a strict GFD show faster and higher rates of gastrointestinal and extraintestinal symptom resolution. Early diagnosis is important to prevent long-term complications such as growth retardation and nutritional deficiencies (2). In this study, children with CD compliant with GFD were evaluated by age, and the relationship between the duration of compliance with diet, anthropometric measurements, and laboratory parameters was determined.

METHODS

A total of 195 CD patients who were followed-up in the pediatric gastroenterology department between January 2000 and December 2018 and who were compliant with GFD for at least 2 years were enrolled in this prospective study. Patients older than 18 years of age, those diagnosed at a different center, and those noncompliant to GFD were excluded from the study.

The diagnosis of CD was based on the ESPGHAN criteria (2). Compliance with GFD was questioned verbally in a standard form, and the patients whose growth improvements were observed at one month of follow-up were considered compliant with GFD.

Clinical and demographic characteristics, laboratory examinations, serological tests, histopathological findings, and genetic analysis of the patients were examined according to age groups at diagnosis and 6th month, 1st, and 2nd year controls.

The application created by the Pediatric Endocrine and Diabetes Association for children (CHILD METRICS) was used for anthropometric measurements of patients at admission and during follow-up. The standard deviation score (SDS) of the patients' height (cm), weight (kg), and body mass index (BMI) were established according to references of Neyzi et al. (4). The patients with a weight below -2 SDS were defined as wasting, -2 to -1 SDS as underweight, 1 to 1 SDS as normal, 1 to 2 SDS as overweight, and those >2 SDS as obese. If the height was <2 SDS, it was regarded as stunted, -2 to -1 SDS as short, -1 to 1 SDS as normal, 1 to 2 SDS as tall, and >2 SDS as very tall. If BMI was <-2, it was defined as malnutrition, -2 to 1 as normal, 1 to 2 as overweight, and >2 as obese (4).

Iron deficiency anemia was based on the Second National Health and Nutrition Examination Survey (NHANES-II) and the Nutrition Committee of the American Academy of Pediatrics (5). Accordingly, the reference values of hemoglobin (Hb) were 10.5 g/dL between 6 months and 2 years of age, 11.5 g/dL between 2 and 12 years of age, 12 g/dL in girls, and 13 g/dL in boys between 12 and 18 years of age. Ferritin levels were significant <12 µg/dL for children ≤5 years and <15 µg/dL for those <5 years. Platelet count <130,000/mm^3 was defined as thrombocytopenia, and >400,000/mm^3 as thrombocytosis (3).

Patients with at least one of the serological tests [antigliadin immunoglobulin A (IgA) and IgG, antiendomisyum IgA and IgG, tissue transglutaminase IgA and IgG] positive were defined as serology positive.

According to the modified Marsh classification (6); grade 0 is defined as normal, grade 1 as intraepithelial lymphocyte increase, grade 2 as intraepithelial lymphocyte increase and crypt hyperplasia, grade 3a as partial villous atrophy, grade 3b as subtotal villous atrophy, and grade 3c as total villous atrophy. Grade ≥2 was considered CD (6).

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Research and Application Center (no: 3207, date: 30.03.2021). Written informed consent was obtained from all parents.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 15.0 package program (SPSS Inc, Chicago, Illinois, U.S.A.). The descriptive statistics were given as numbers and percentages for categorical variables and as mean, standard deviation, and median for numerical variables. Repeated measures variance analysis was used in analysis of numerical variables in dependent groups when the differences satisfy normal distribution, and if it was not met, the Friedman test was used. Analysis of subgroups was performed using the Wilcoxon test and interpreted with Bonferroni correction. The rates in the dependent groups were compared using Cochran's Q test. Analysis of subgroups was performed using the McNemar test and interpreted with Bonferroni correction. P<0.05 was considered significant for all results.

RESULTS

The mean age of patients with CD was 7.3±4.4 (range 0-17 years), and the male/female ratio was 0.69. Of the patients, 19.5% were diagnosed at ≤2 years old, 8.2% were 3-4 years old, 42.1% were 5-9 years old, 24.6% were 10-14 years old, and 5.6% were ≥15 years old. The most common complaint at admission was growth retardation (44.6%), followed by diarrhea (29.7%), abdominal pain (21%), and abdominal distention (18.5%). When the complaints at admission were evaluated by age group, it was found that diarrhea (60.5%) and abdominal distention (36.8%) were higher in patients ≤2 years of age than in the other age groups (p<0.001 and p=0.025, respectively). The clinical and demographic characteristics and laboratory findings of the patients according to age groups are shown in Table 1.

68.2% of the patients had typical, 26.2% had atypical, and 5.6% had asymptomatic CD. 10% of asymptomatic CD patients had a family history and were referred to us for screening. 20.5% of the patients had accompanying disease, of which the most common was type 1 diabetes mellitus (3.1%), followed by protein losing enteropathy (2.5%). The most common accompanying genetic diseases were Down syndrome (1%) and Turner syndrome (1%).

When the patients were classified according to height SDSs, no significant difference was observed between height SDSs at diagnosis and 6 months of follow-up (p=0.22). In total, 37.4% of the patients stunted at diagnosis, 33.8% at 6 months of follow-up, 28.7% at 1st year, and 18.5% at 2nd year (Table 2). According to weight SDSs, no statistically significant differences were observed at diagnosis, 6 months, 1st year, and 2nd year of follow-up. As the duration of compliance to GFD increased, the number of patients who were normal and overweight increased and those who were underweight decreased (Table 2). In addition, a significant difference was observed in BMI Z-scores during follow-up (Table 2).

Table 1. The clinical and demographic characteristics, and laboratory findings of the patients with celiac disease according to age groups

	≤2 years (n=38)	3-4 years (n=16)	5-9 years (n=82)	10-14 years (n=48)	≥15 years (n=11)	p-value
Gender (M/F)	0.58 (14/24)	1 (8/8)	0.6 (31/51)	0.7 (21/27)	1.2 (6/5)	0.71
Complaint admission						
Gastrointestinal						
Growth retardation	15 (39.5%)	9 (56.3%)	30 (36.6%)	29 (60.4%)	4 (36.4%)	0.07
Diarrhea	23 (60.5%)	7 (43.8%)	17 (20.7%)	9 (18.8%)	2 (18.2%)	<0.001
Abdominal pain	4 (10.5%)	4 (25%)	20 (24.4%)	11 (22.9%)	2 (18.2%)	0.49
Abdominal distention	14 (36.8%)	3 (18.8%)	12 (14.6%)	6 (12.5%)	1 (9.1%)	0.025
Poor weight gain	6 (15.8%)	3 (18.8%)	12 (14.6%)	4 (8.3%)	1 (9.1%)	0.74
Constipation	3 (7.9%)	2 (12.5%)	13 (15.9%)	5 (10.4%)	-	0.61
Nausea	3 (7.9%)	-	4 (4.9%)	4 (8.3%)	1 (9.1%)	0.68
Poor appetite	2 (5.3%)	1 (6.3%)	7 (8.5%)	-	-	0.22
Vomiting	1 (2.6%)	1 (6.3%)	3 (3.7%)	1 (2.1%)	-	0.82
Extraintestinal						
Refractory anemia	2 (5.3%)	2 (12.5%)	11 (13.4%)	12 (25%)	3 (27.3%)	0.07
Short stature	1 (2.6%)	-	5 (6.1%)	3 (6.3%)	1 (9.1%)	0.73
Fatigue	1 (2.6%)	-	2 (2.4%)	1 (2.1%)	-	1.00
Other	-	-	2 (2.4%)	1 (2.1%)	-	1.00
Screening	1 (2.6%)	-	6 (7.3%)	2 (4.2%)	1 (9.1%)	0.65

Table 1. Continued

	≤2 years (n=38)	3-4 years (n=16)	5-9 years (n=82)	10-14 years (n=48)	≥15 years (n=11)	p-value
Type of disease						
Typical	27 (71.1%)	12 (75%)	52 (63.4%)	35 (72.9%)	7 (63.6%)	0.89
Atypical	10 (26.3%)	4 (25%)	23 (28%)	11 (22.9%)	3 (27.3%)	
Asymptomatic	1 (2.6%)	-	7 (8.5%)	2 (4.2%)	1 (9.1%)	
Marsh classification						
Grade 1	-	-	-	-	-	0.82
Grade 2	4 (10.5%)	-	3 (3.7%)	1 (2.1%)	-	
Grade 3a	10 (26.3%)	3 (18.8%)	19 (23.2%)	10 (20.8%)	4 (36.4%)	
Grade 3b	14 (36.8%)	9 (56.3%)	36 (43.9%)	26 (54.2%)	5 (45.5%)	
Grade 3c	10 (26.3%)	4 (25%)	24 (29.3%)	11 (22.9%)	2 (18.2%)	
Hemoglobin (g/dL)						
Normal	20 (52.6%)	4 (25%)	41 (50%)	24 (50%)	6 (54.5%)	0.39
Low	18 (47.4%)	12 (75%)	41 (50%)	24 (50%)	5 (45.5%)	
Hematocrit (%)						
Normal	21 (55.3%)	4 (25%)	37 (45.1%)	24 (50%)	7 (63.6%)	0.23
Low	17 (44.7%)	12 (75%)	45 (54.9%)	24 (50%)	4 (36.4%)	
MCV						
Normal	25 (65.8%)	8 (50%)	35 (42.7%)	25 (52.1%)	5 (45.5%)	0.22
Low	13 (34.2%)	8 (50%)	47 (57.3%)	23 (47.9%)	6 (54.5%)	
Platelet count						
Normal	22 (57.9%)	10 (62.5%)	54 (65.9%)	45 (93.8%)	10 (90.9%)	<0.001
High	16 (42.1%)	6 (37.5%)	27 (32.9%)	2 (4.2%)	1 (9.1%)	
Low	-	-	1 (1.2%)	1 (1.2%)	-	
Serology						
At diagnosis						
Positive	38 (100%)	16 (100%)	81(98.8%)	47 (97.9%)	11 (100%)	1.00
Negative	-	-	1 (1.2%)	1 (2.1%)	-	
At 6th months						
Positive	23 (60.5%)	11 (68.8%)	57 (69.5%)	36 (75%)	7 (63.7%)	0.69
Negative	15 (39.5%)	5 (31.3%)	25 (30.5%)	12 (25%)	4 (36.4%)	
At 1st year						
Positive	14 (36.8%)	6 (37.5%)	31 (37.8%)	25 (52.1%)	4 (36.4%)	0.52
Negative	24 (63.2%)	10 (62.5%)	51 (62.2%)	23 (47.9%)	7 (63.6%)	
At 2nd year						
Positive	10 (26.3%)	3 (18.8%)	16 (19.5%)	13 (27.1%)	1 (9.1%)	0.62
Negative	28 (73.7%)	13 (81.3%)	66 (80.5%)	35 (72.9%)	10 (90.9%)	

MCV: Mean corpuscular volume, M/F: Male/female
P<0.05 is statistically significant

51.7% of the patients with height <-2 SDS had growth retardation at admission (p<0.001). No significant differences were observed in terms of complaints at admission and height SDSs, except that 40% of the patients who were diagnosed with CD at screening had normal height (p=0.003) (Table 3). When the complaint at diagnosis and weight SDSs were evaluated, it was observed that the patients with growth retardation and diarrhea were mostly wasting and underweight patients (p<0.001, p=0.038, respectively) (Table 4). It was remarkable that the patients with constipation were of normal weight (p=0.03). No statistically significant differences were found between

Table 2. Evaluation of patients' height, weight, and BMI SDS, and laboratory parameters according to compliance to diet

	Diagnosis	6th months	1st year	2nd year	p-value
Height (SDS)					
Stunted (<-2)	73 (37.4%)	66 (33.8%)	56 (28.7%)	36 (18.5%)	<0.001
Short stature (-2 and -1)	51 (26.2%)	51 (26.2%)	48 (24.6%)	56 (28.7%)	
Normal (-1 and 1)	58 (29.7%)	65 (33.3%)	74 (37.9%)	81 (41.5%)	
Tall (1 and 2)	11 (5.6%)	10 (5.1%)	15 (7.7%)	18 (9.2%)	
Very tall (>2)	2 (1%)	3 (1.5%)	2 (1%)	4 (2.1%)	
Weight (SDS)					
Wasting (<-2)	71 (36.4%)	51 (26.2%)	35 (17.9%)	32 (16.4%)	<0.001
Underweight (-2 and -1)	52 (26.7%)	55 (28.2%)	52 (26.7%)	44 (22.6%)	
Normal (-1 and 1)	64 (32.8%)	79 (40.5%)	92 (47.2%)	100 (51.3%)	
Overweight (1 and 2)	7 (3.6%)	9 (4.6%)	15 (7.7%)	18 (9.2%)	
Obese (>2)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	
BMI (SDS)					
Malnutrition (<-2)	36 (18.5%)	12 (6.2%)	13 (6.7)	15 (7.7%)	<0.001
Normal (-2 and 1)	152 (77.9%)	164 (84.1%)	153 (78.5%)	163 (83.6%)	
Overweight (1 and 2)	6 (3.1%)	18 (9.2%)	25 (12.8%)	16 (8.2%)	
Obese (>2)	1 (0.5%)	1 (0.5%)	4 (2.1%)	1 (0.5%)	
Hemoglobin (g/dL)					
Normal	95 (48.7%)	133 (68.2%)	151 (77.4%)	164 (84.1%)	<0.001
Low	100 (51.3%)	62 (31.8%)	44 (22.6%)	31 (15.9%)	
Hematocrit (%)					
Normal	93 (47.7%)	137 (70.3%)	152 (77.9%)	170 (87.2%)	<0.001
Low	102 (52.3%)	58 (29.7%)	43 (22.1%)	25 (12.8%)	
MCV (fL/dL)					
Normal	98 (50.3%)	120 (61.5%)	143 (73.3%)	162 (83%)	<0.001
Low	97 (49.7%)	75 (38.5%)	52 (26.7%)	33 (16.9%)	
Ferritin					
Normal	74 (37.9%)	114 (58.5%)	127 (65.1%)	144 (73.8%)	<0.001
Low	121 (62.1%)	81 (41.5%)	68 (34.9%)	51 (26.2%)	
Vitamin B12					
Normal	192 (98.5%)	193 (99.5%)	194 (99.5%)	194 (99.5%)	0.57
Low	3 (1.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	
Folic acid					
Normal	174 (89.2%)	189 (96.9%)	194 (99.5%)	193 (99%)	<0.001
Low	21 (10.8%)	6 (3.1%)	1 (0.5%)	2 (1%)	

BMI: Body mass index, MCV: Mean corpuscular volume, SDS: Standard deviation score
P<0.05 is statistically significant

other complaints at diagnosis and weight SDSs (p<0.05) (Table 4).

51.3% of the patients had Hb levels lower than the reference range according to age and 50.3% of the patients had mean corpuscular volume (MCV) levels lower than the reference range according to age. 26.7% had thrombocytosis, whereas only two patients had thrombocytopenia. 42.1% of the patients ≤2 years of age had thrombocytosis (p<0.001).

The comparison of Hb, MCV, and platelet counts according to age groups is shown in Table 1 and according to follow-up periods in Table 2. When the patients with low ferritin at diagnosis evaluated, a significant decrease in the number of patients was observed during follow-up (p<0.001) (Table 2).

None of the patients had an IgA deficiency. It was found to be statistically significant that the number of patients with positive serology started to decrease and became

Table 3. Comparison of complaints at admissions according to height SDS

	Stunted (<-2 SDS)	Short stature (-2 and -1 SDS)	Normal (-1 and 1 SDS)	Tall (1 and 2 SDS)	Very tall (>2 SDS)	p-value
Gastrointestinal						
Growth retardation						
No	28 (25.9%)	24 (22.2%)	44 (40.7%)	10 (9.3%)	2 (1.9%)	<0.001
Yes	45 (51.7%)	27 (31%)	14 (16.1%)	1 (1.1%)	-	
Diarrhea						
No	49 (35.8%)	32 (23.4%)	47 (34.3%)	7 (5.1%)	2 (1.5%)	0.19
Yes	24 (41.4%)	19 (32.8%)	11 (19%)	4 (6.9%)	-	
Abdominal pain						
No	62 (40.3%)	39 (25.3%)	42 (27.3%)	10 (6.5%)	1 (0.6%)	0.22
Yes	11 (26.8%)	12 (29.3%)	16 (39%)	1 (2.4%)	1 (2.4%)	
Abdominal distention						
No	59 (37.1%)	41 (25.8%)	46 (28.9%)	11 (6.9%)	2 (1.3%)	0.6
Yes	14 (38.9%)	10 (27.8%)	12 (33.3%)	-	-	
Poor weight gain						
No	65 (38.5%)	43 (25.4%)	49 (29%)	10 (5.9%)	2 (1.2%)	0.87
Yes	8 (30.8%)	8 (30.8%)	9 (34.6%)	1 (3.8%)	-	
Constipation						
No	67 (39%)	47 (27.3%)	49 (28.5%)	8 (4.7%)	1 (0.6%)	0.08
Yes	6 (26.1%)	4 (17.4%)	9 (39.1%)	3 (13%)	1 (4.3%)	
Nausea						
No	69 (37.7%)	46 (25.1%)	56 (30.6%)	10 (5.5%)	2 (1.1%)	0.51
Yes	4 (33.3%)	5 (41.7%)	2 (16.7%)	1 (8.3%)	-	
Poor appetite						
No	71 (38.4%)	47 (25.4%)	56 (30.3%)	9 (4.9%)	2 (1.1%)	0.18
Yes	2 (20%)	4 (40%)	2 (20%)	2 (20%)	-	
Vomiting						
No	69 (36.5%)	50 (26.5%)	58 (30.7%)	10 (5.3%)	2 (1.1%)	0.17
Yes	4 (66.7%)	1 (16.7%)	-	1 (16.7%)	-	
Extraintestinal						
Refractory anemia						
No	64 (38.8%)	41 (24.8%)	48 (29.1%)	10 (6.1%)	2 (1.2%)	0.77
Yes	9 (30%)	10 (33.3%)	10 (33.3%)	1 (3.3%)	-	
Short stature						
No	69 (37.3%)	49 (26.5%)	55 (29.7%)	10 (5.4%)	2 (1.1%)	0.8
Yes	4 (40%)	2 (20%)	3 (30%)	1 (10%)	-	
Fatigue						
No	71 (37.2%)	50 (26.2%)	58 (30.4%)	10 (5.2%)	2 (1%)	0.22
Yes	2 (50%)	1 (25%)	-	1 (25%)	-	
Other						
No	72 (37.5%)	51 (26.6%)	56 (29.2%)	11 (5.7%)	2 (1%	0.58
Yes	1 (33.3%)	-	2 (66.7%)	-	-	
Screening						
No	71 (38.4%)	51 (27.6%)	53 (28.6%)	9 (4.9%)	1 (0.5%)	0.004
Yes	2 (20%)	-	5 (50%)	2 (20%)	1 (10%)	

SDS: Standard deviation score, p<0.05 is statistically significant

Table 4. Comparison of complaints at admissions according to weight SDS

	Wasting (<-2 SDS)	Underweight (-2 and -1 SDS)	Normal (-1 and 1 SDS)	Overweight (1 and 2 SDS	Obese (>2 SDS)	p-value
Gastrointestinal						
Growth retardation						
No	28	23 (21.3%)	50 (46.3%)	6 (5.6%)	1 (0.9%)	<0.001
Yes	43 (25.9%)	29 (33.3%)	14 (16.1%)	1 (1.1%)	-	
Diarrhea						
No	41(29.9%)	42 (30.7%)	47(34.3%)	6 (4.4%)	1 (0.7%)	0.038
Yes	30 (51.7%)	10 (17.2%)	17 (29.3%)	1 (1.7%)	-	
Abdominal pain						
No	60 (39%)	40 (26%)	49 (31.8%)	4 (2.6%)	1 (0.6%)	0.36
Yes	11 (26.8%)	12 (29.3)	15 (36.6%)	3 (7.3%)	-	
Abdominal distention						
No	54 (34%)	48 (30.2%)	49 (30.8%)	7 (4.4%)	1 (0.6%)	0.06
Yes	17 (47.2%)	4 (11.1%)	15 (41.7%)	-	-	
Poor weight gain						
No	63 (37.3%)	44 (26%)	54 (32%)	7 (4.1%)	1 (0.6%)	0.80
Yes	8 (30.8%)	8 (30.8%)	10 (38.5%)	-	-	
Constipation						
No	68 (39.5%)	46 (26.7%)	52 (30.2%)	5 (2.9%)	1 (0.6%)	0.03
Yes	3 (13%)	6 (26.1%)	12 (52.2%)	2 (8.7%)	-	
Nausea						
No	68 (37.2%)	49 (26.8%)	58 (31.7%)	7 (3.8%)	1 (0.5%)	0.67
Yes	3 (25%)	3 (25%)	6 (50%)	-	-	
Poor appetite						
No	68 (36.8%)	47 (25.4%)	63 (34.1%)	6 (3.2%)	1 (0.5%)	0.16
Yes	3 (30%)	5 (50%)	1 (10%)	1 (10%)	-	
Vomiting						
No	69 (36.5%)	49 (25.9%)	63 (33.3%)	7 (3.7%)	1 (0.5%)	0.63
Yes	2 (33.3%)	3 (50%)	1 (16.7%)	-	-	
Extraintestinal						
Refractory anemia						
No	60 (36.4%)	44 (26.7%)	53 (32.1%)	7 (4.2%)	1 (0.6%)	0.90
Yes	11 (36.7%)	8 (26.7%)	11 (36.7%)	-	-	
Short stature						
No	66 (35.7%)	50 (27%)	61 (33%)	7 (3.8%)	1 (0.5%)	0.85
Yes	5 (50%)	2 (20%)	3 (30%)	-	-	
Fatigue						
No	69 (36.1%)	51 (26.7%)	63 (33%)	7 (3.7%)	1 (0.5%)	1.00
Yes	2 (50%)	1 (25%)	1 (25%)	-	-	
Other						
No	71 (37%)	52 (27.1%)	61 (31.8%)	7 (3.6%)	1 (0.5%)	0.17
Yes	-	-	3 (100%)	-	-	
Screening						
No	70 (37.8%)	50 (27%)	60 (32.4%)	5 (2.7%)	-	
Yes	1 (10%)	2 (20%)	4 (40%)	2 (20%)	1 (10%)	0.003

SDS: Standard deviation score, p<0.05 is statistically significant

negative related with the compliance to diet during follow-up ($p<0.001$). Although the rate of patients with negative serology increased among age groups, the difference was not statistically significant (Table 2). Serology did not differ by gender and laboratory parameters such as Hb, hematocrit, MCV, and vitamin B12 levels at the time of diagnosis, 6 months, 1st year, and 2nd year ($p>0.05$), except for ferritin and folic acid levels. Ferritin levels at 6 months were significantly lower in patients with positive serology than in those with negative serology ($p=0.047$), and normal levels were higher in patients with negative serology at 1 year ($p=0.03$). In patients with negative serology, folic acid levels were significantly within normal limits at the 2nd year ($p=0.048$).

HLA typing was performed in 111 patients and revealed that 58.6% of those had HLA DQ2, 20.7% had HLA DQ8, 10.8% had both HLA DQ2 and HLA DQ8 positivity, and only 9.9% had both HLA DQ2 and HLA DQ8 negativity. No significant differences were observed, except that asymptomatic patients diagnosed during screening had higher positivity for both HLA DQ2 and HLA DQ8 compared with the other HLA groups ($p=0.01$).

DISCUSSION

In recent studies on CD, it has been reported that the mean age of the patients at diagnosis was increased (7-9). Similarly, the mean age of our patients was 7.3±4.4 years and 42% of those patients were 5-9 years of age. Increased age at diagnosis is thought to be due to increased awareness of the disease, widespread screening, and earlier diagnosis of patients presenting with atypical symptoms.

Similar to other studies (7,9) reporting female predominance (67% and 68.6%, respectively), 58.9% of the patients were girls in our study. CD is more common in females because autoimmune diseases are more common in females, they have more hospital admissions and examinations, and they are more symptomatic than males (10). We found no significant difference in gender according to age groups, similar to the study by Tanpowpong et al. (11).

A family history of CD was found in 6.9% and 18% of the patients in the studies of Oliveira et al. (9) and Stone et al. (8), respectively. In total, 8.7% of our patients had a family history. Oliveira et al. (9) reported that the most common presenting symptom was abdominal pain, followed by diarrhea, growth retardation, and abdominal distention. They also observed that diarrhea and abdominal distention were significantly more common in patients younger than 5 years and abdominal pain in children older than 5 years (9). Van Kalleveen et al. (7) reported that abdominal distention (72.1%), growth retardation (60.5%), and diarrhea (48.8%) among 0-3 years of age, abdominal pain (37.2%), fatigue (36%), and short stature (22%) among 4-12 years of ages, abdominal pain (83.3%) among patients older than 12 years of age were the most common when the symptoms were evaluated according to age groups. In our study, the most common presenting symptom was growth retardation (44.6%), followed by diarrhea (29.7%), and abdominal pain (21%). Although growth failure and diarrhea were common in our children ≤2 years, similar to the literature, our study differed from those studies in that the most common symptoms were atypical symptoms such as refractory anemia and short stature as age increased. It has been shown that long-term breastfeeding, addition of very small amounts of gluten-containing foods to the diet <12 months, and continuation of breast milk when starting to give foods containing gluten reduce the risk of developing CD in children <2 years (12). Breastfeeding was not questioned in our study.

The most common type of disease was the classical type in our study, consistent with other studies (9,13). It has been reported that most of the patients had Marsh 3 classification in their histopathological examination in studies conducted by Ziv-Baran et al. (14), Vivas et al. (15), and Oliveira et al. (9). Tanpowpong et al. (11) reported that villous atrophy is more common between 0 and 5 years of age. In our study, histopathological examinations of the patients revealed Marsh grade 3, but no statistically significant difference was obtained according to age groups, similar to the study of Vivas et al. (15).

Sansotta et al. (16) evaluated the relationship between anthropometric measurements of CD patients at diagnosis and during follow-up and response to GFD. They observed that both height and weight SDSs measured at follow-ups after starting the diet significantly increased; however, the increase in BMI did not make a statistical difference. Więch et al. (17) reported a significant difference only in weight SDSs and not in height and BMI SDSs. They observed that the increase in height was higher in patients compliant with GFD than in the uncompliant group, but the difference was not significant, whereas the difference in weight gain was statistically significant between these groups. In our study, both height and weight SDSs were found to be increased during follow-up in patients compliant with GFD, and increased numbers of normal weight and overweight children were observed.

It has been stated that the best way to evaluate the developmental delay of patients following a GFD is by BMI (18,19). Valletta et al. (18) compared BMI Z-scores at

the time of diagnosis and 1 year after starting GFD and found that the number of overweight children significantly increased with compliance to GFD (11% to 21%). Cheng et al. (19) reported that 66% of their patients on GFD who were underweight gained weight, whereas 54% of overweight and 47% of obese patients lost weight. In our study, the number of malnourished patients decreased, and the number of normal weight and overweight patients increased while on GFD. Although the number of obese patients in our study did not change, it should be noted that the number of overweight and obese patients increased immediately both at diagnosis and with dietary compliance (18,19).

Abnormalities in platelet counts have been reported to be secondary to iron deficiency anemia, hyposplenism, and/or inflammatory mediators (20). Thrombocytosis is more common than thrombocytopenia and is normalized with GFD (20). Bansal et al. (21) and Çatal et al. (22) reported that 33% and 16.5% of their patients had thrombocytosis, respectively, and stated a significant improvement in thrombocytosis with GFD. It was remarkable that a significant difference was observed in thrombocytosis among the age groups in our study, especially ≤2 years of age.

It has been reported that iron deficiency anemia is common in CD patients and may sometimes be the only presenting symptom of the disease. Additionally, Hb levels may not be normal for up to 1 year and iron stores are low for up to 2 years despite GFD and iron supplementation (23). Although we observed that ferritin levels increased as the duration of compliance to GFD was prolonged, especially in the 6th month-2nd year of follow-up, it was not statistically significant. Ferritin levels were low in 34.9% of the patients in the first year and 26.2% of our patients in the second year of follow-up.

Vitamin and mineral deficiencies have been reported to decrease with compliance with GFD (24). In our study, vitamin B12 deficiency was detected in only three patients at the time of diagnosis. Folate deficiency was higher and its decrease with GFD was consistent with the literature.

Histopathological recovery of CD is faster in children than in adults, with a complete recovery rate of 88-96% over 2 years (25). In our study, it was determined that 31% of the patients on GFD at 6 months, 58.9% at 1st year, and 77.9% at 2nd year of follow-up had negative serology, consistent with the study conducted by Gidrewicz et al. (26). No significant differences were obtained in serological results between age groups in our study, which may be due to unequal distribution of patients and non-standardized serological parameters among patients.

It has been reported that most patients with CD have HLA DQ2 positivity, followed by HLA DQ8 (9,27). The rates of both HLA DQ2 and HLA DQ8 positivity were reported to be 11% and 42.9%, respectively (9,27). Similarly, 58.6% of our patients had HLA DQ2 positivity. HLA tissue typing has a high negative predictive value (28). However, 9.9% of our patients, those who had tissue transglutaminase levels at least 10 times higher and Marsh 2 and 3 (a, b, c) grades, were negative for both HLA DQ2 and HLA DQ8, a higher rate than that reported in the literature. It has been stated that the disease has a more serious course in HLA DQ2-positive patients than in DQ8-positive patients; even DQ2.5 homozygous alleles had clinically more severe disease, serological titers, and Marsh classification than the other alleles (27,29,30). No statistically significant differences were obtained between HLA typing and Marsh grades according to age groups in our study, which may be related to the lower number of HLA DQ2-positive patients than in other studies.

The limitations of this study were being a single-center retrospective study, unavailability of determining HLA alleles, and non-standardized serological parameters among patients.

CONCLUSION

In conclusion, we observed an increase in the number of patients diagnosed at older ages with atypical symptoms. As the duration of compliance to GFD increases, the number of overweight patients increases and the normalization of anthropometric measurements. Therefore, early diagnosis of CD and maintenance of compliance with GFD are essential because of gradual improvement in both laboratory and anthropometric measurements observed in patients compliant with GFD.

ETHICS

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Research and Application Center (no: 3207, date: 30.03.2021).

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

Authorship Contributions

Surgical and Medical Practices: B.Ö.A., N.U., M.U., D.G., Concept: B.Ö.A., N.U., Design: B.Ö.A., N.U., Data Collection or Processing: B.Ö.A., N.U., M.U., D.G., Analysis or Interpretation: B.Ö.A., N.U., M.U., D.G., Literature Search: B.Ö.A., N.U., Writing: B.Ö.A., N.U.

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

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

REFERENCES

1. Sahin Y. Celiac disease in children: A review of the literature. World J Clin Pediatr 2021;10:53-71.
2. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr. 2012;54:136-60.
3. Sciurti M, Fornaroli F, Gaiani F, Bonaguri C, Leandro G, Di Mario F, et al. Genetic susceptibilty and celiac disease: What role do HLA haplotypes play? Acta Biomed 2018;89:17-21.
4. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol 2015;7:280-93.
5. Goddard WP, Murray I, Long RG. Iron deficiency anaemia. Gastrointestinal endoscopy should always be used. BMJ 1997;314:1760.
6. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol 1999;11:1185-94.
7. Van Kalleveen MW, de Meij T, Plötz FB. Clinical spectrum of paediatric coeliac disease: a 10-year single-centre experience. Eur J Pediatr 2018;177:593-602.
8. Stone ML, Bohane TD, Whitten KE, Tobias VH, Day AS. Age related clinical features of childhood coeliac disease in Australia. BMC Pediatr 2005;5:11.
9. Oliveira GN, Mohan R, Fagbemi A. Review of Celiac Disease Presentation in a Pediatric Tertiary Centre. Arq Gastroenterol 2018;55:86-93.
10. Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya JM. Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. J Autoimmun 2012;38:109-19.
11. Tanpowpong P, Broder-Fingert S, Katz AJ, Camargo CA Jr. Age-related patterns in clinical presentations and gluten-related issues among children and adolescents with celiac disease. Clin Transl Gastroenterol 2012;3:e9.
12. Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. Am J Clin Nutr 2002;75:914-21.
13. Imran, Cheema HA, Alvi MA, Rehman MU, Ali M, Sarwar HA. Spectrum of Clinical Presentation of Celiac Disease in Pediatric Population. Cureus 2021;10;13:e15582.
14. Ziv-Baran T, Dubov Y, Weinberger R, Guz-Mark A, Shamir R, Assa A. Anti-tissue transglutaminase titers are associated with endoscopic findings and severity of mucosal damage in children with celiac disease. Eur J Pediatr 2021;180:263-9.
15. Vivas S, Ruiz de Morales JM, Fernandez M, Hernando M, Herrero B, Casqueiro J, et al. Age related clinical, serological, and histopathological features of celiac disease. Am J Gastroenterol 2008;103:2360-5.
16. Sansotta N, Guandalini S, Romano S, Amirikian K, Cipolli M, Tridello G, et al. The gluten free diet's impact on growth in children with celiac disease in two different countries. Nutrients 2020;12:1547.
17. Więch P, Chmiel Z, Bazaliński D, Sałacińska I, Bartosiewicz A, Mazur A, et al. The Relationship between Body Composition and a Gluten Free Diet in Children with Celiac Disease. Nutrients 2018;10:1817.
18. Valletta E, Fornaro M, Cipolli M, Conte S, Bissolo F, Danchielli C. Celiac disease and obesity: need for nutritional follow-up after diagnosis. Eur J Clin Nutr 2010;64:1371-2.
19. Cheng J, Brar PS, Lee AR, Green PH. Body mass index in celiac disease: beneficial effect of a gluten-free diet. J Clin Gastroenterol 2010;44:267-71.
20. Baydoun A, Maakaron JE, Halawi H, Abou Rahal J, Taher AT. Hematological manifestations of celiac disease. Scand J Gastroenterol 2012;47:1401-11.
21. Bansal D, Trehan A, Gupta MK, Varma N, Marwaha RK. Serodiagnosis of celiac disease in children referred for evaluation of anemia: a pediatric hematology unit's experience. Indian J Pathol Microbiol 2011;54:756-60.
22. Çatal F, Topal E, Ermiştekin H, Yildirim Acar N, Sinanoğlu MS, Karabiber H, et al. The hematologic manifestations of pediatric celiac disease at the time of diagnosis and efficiency of gluten-free diet. Turkish J Med Sci 2015;45:663-7.
23. Efthymakis K, Milano A, Laterza F, Serio M, Neri M. Iron deficiency anemia despite effective gluten-free diet in celiac disease: Diagnostic role of small bowel capsule endoscopy. Dig Liver Dis 2017;49:412-6.
24. Deora V, Aylward N, Sokoro A, El-Matary W. Serum Vitamins and Minerals at Diagnosis and Follow-up in Children With Celiac Disease. J Pediatr Gastroenterol Nutr 2017;65:185-9.
25. Vécsei E, Steinwendner S, Kogler H, Innerhofer A, Hammer K, Haas OA, et al. Follow-up of pediatric celiac disease: Value of antibodies in predicting mucosal healing, a prospective cohort study. BMC Gastroenterol 2014;14:28.
26. Gidrewicz D, Trevenen CL, Lyon M, Butzner JD. Normalization Time of Celiac Serology in Children on a Gluten-free Diet. J Pediatr Gastroenterol Nutr 2017;64:362-7.
27. Szałowska-Woźniak DA, Bąk-Romaniszyn L, Cywińska-Bernas A, Zeman K. Evaluation of HLA-DQ2/DQ8 genotype in patients with celiac disease hospitalised in 2012 at the Department of Paediatrics. Prz Gastroenterol 2014;9:32-7.
28. Hadithi M, von Blomberg BM, Crusius JB, Bloemena E, Kostense PJ, Meijer JW, et al. Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. Ann Intern Med 2007;147:294-302.
29. Martínez-Ojinaga E, Fernández-Prieto M, Molina M, Polanco I, Urcelay E, Núñez C. Influence of HLA on clinical and analytical features of pediatric celiac disease. BMC Gastroenterol 2019;19:91.
30. Ramosaj-Morina A, Burek Kamenaric M, Azemi M, Spahiu L, Grubic Z, Zunec R. HLA Haplotype Association with Celiac Disease in Albanian Pediatric Patients from Kosovo. Gastroenterol Res Pract 2019;2019:7369014.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:152-158
DOI: 10.4274/BMJ.galenos.2024.2024.2-10

Research

The Impact of the COVID-19 Pandemic on Orthopedic Trauma Management; A Cross-sectional Study

COVİD-19 Pandemisinin Ortopedik Travma Yönetimi Üzerindeki Etkisi; Kesitsel Bir Çalışma

Vedat Öztürk[1], Başar Burak Çakmur[2], Ali Can Koluman[1], Malik Çelik[1], Altuğ Duramaz[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye

ABSTRACT

Objective: The aim of this study was to compare emergency orthopedic trauma admissions between the pre- and pandemic periods and detect changes in orthopedic trauma epidemiology.

Methods: A total of 40,700 patients admitted within 1 year between March 2019 and March 2020 comprised the pre-pandemic group and 16,935 patients admitted between March 2020 and March 2021 comprised the pandemic group. Demographic characteristics of the patients, such as age and gender, were recorded. In addition, the injury mechanisms of the patients, diagnosis, injured extremity or anatomical region, broken bone, fracture classification, multitrauma rates, trauma-related complications, hospitalization days, and treatment modalities were examined.

Results: In the pre-pandemic period, the mean age of the patients was younger, and the distributions of pediatric/adolescent patients and female patients were higher compared with the pandemic period (p=0.001, p=0.001, and p=0.001; respectively). Fractures and dislocations were more frequent in the pandemic period, whereas soft tissue injuries were more common in the pre-pandemic period (p=0.001). Home accidents increased and occupational accidents decreased during the pandemic period (p=0.001). The rate of surgical treatment statistically increased during the pandemic period (p=0.001).

Conclusion: Considering the epidemiology of orthopedic trauma, estimating the trauma burden and optimizing resource use and allocation are very important for maintaining safe and effective treatment services for patients in extraordinary situations such as the coronavirus disease-2019 pandemic, which can cause serious disruptions in the healthcare system.

Keywords: Orthopedic trauma, COVID-19, pandemic, trauma epidemiology, resource use

ÖZ

Amaç: Çalışmanın amacı, pandemi öncesi dönem ile pandemi dönemi arasında acil ortopedik travma başvurularını karşılaştırmak ve ortopedik travma epidemiyolojisindeki değişiklikleri tespit etmektir.

Gereç ve Yöntem: Mart 2019 ile Mart 2020 arasında 1 yıl içinde başvuran 40.700 hasta pandemi öncesi grubu oluştururken, Mart 2020 ile Mart 2021 arasında başvuran 16.935 hasta pandemi grubunu oluşturmaktadır. Hastaların demografik özellikleri, yaş ve cinsiyet gibi, kaydedilmiştir. Ayrıca, hastaların yaralanma mekanizmaları, tanı, yaralanan ekstremite veya anatomik bölge, kırılan kemik, kırık sınıflandırması, çoklu travma oranları, travma ile ilişkili komplikasyonlar, hastanede yatış günleri ve tedavi yöntemleri incelenmiştir.

Bulgular: Pandemi öncesi dönemde, hastaların ortalama yaşı daha gençti ve pediatrik/adölesan hastalar ile kadın hastaların dağılımları pandemi dönemine kıyasla daha yüksekti (sırasıyla p=0,001, p=0,001 ve p=0,001). Pandemi döneminde kırıklar ve çıkıklar daha sık görülürken, pandemi öncesi dönemde yumuşak doku yaralanmaları daha yaygındı (p=0,001). Ev kazaları pandemi döneminde artarken, iş kazaları azalmıştır (p=0,001). Cerrahi tedavi oranı istatistiksel olarak pandemi döneminde artmıştır (p=0,001).

Sonuç: Ortopedik travmanın epidemiyolojisini göz önünde bulundurarak, travma yükünü tahmin edebilmek ve kaynak kullanımını ve tahsisini optimize etmek, koronavirüs hastalığı-2019 pandemisi gibi olağanüstü durumlarda sağlık sisteminde ciddi aksamalara neden olabilecek hastalar için güvenli ve etkili tedavi hizmetlerini sürdürebilmek açısından oldukça önemlidir.

Anahtar Kelimeler: Ortopedik travma, COVİD-19, pandemi, travma epidemiyolojisi, kaynak kullanımı

Address for Correspondence: Vedat Öztürk, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye
Phone: +90 537 231 43 17 E-mail: dr.ozturkvedat@gmail.com ORCID ID: orcid.org/0000-0003-2412-9725

Cite as: Öztürk V, Çakmur BB, Koluman AC, Çelik M, Duramaz A. The Impact of the COVID-19 Pandemic on Orthopedic Trauma Management; A Cross-sectional Study. Med J Bakirkoy 2024;20:152-158

Received: 26.02.2024
Accepted: 10.06.2024

INTRODUCTION

Although the coronavirus disease-2019 (COVID-19) pandemic seems to be under control, it continues to be a global problem for all world societies and our health systems because of the new forms (such as Erise variant) that have emerged and the fact that the disease has not yet been fully eradicated (1). Similar to many countries, our government has taken many measures to prevent the spread of the pandemic. Several rigid restrictions were taken to prevent possible blockages in the healthcare system and uncontrolled deaths, especially in the early stages of the pandemic when the vaccine was not yet widespread. Lockdown except for emergencies, closing schools and switching to online education, closing workplaces and developing remote working models, and banning social events and crowded activities were among the main precautions taken to reduce social contact and prevent the rapid spread of the pandemic (2,3). These precautions significantly affected social mobility. Especially during periods of strict isolation, traffic and human mobility decreased to a minimum level with lockdowns (4,5).

However, a large number of health institutions were privatized to combat infection, prevent the spread of the pandemic and ensure adequate resource allocation. Despite these regulations, there were serious resource problems in basic health services (6). Outpatient services, except for emergency health services, were either partially or completely stopped depending on the period of the pandemic (2,7). The precautions and the decrease in social mobility brought about by the precautions led to serious changes in the demand in the healthcare system. The healthcare system reaching saturation due to increasing COVID-19 cases and the filling of intensive care units and inpatient services with COVID-19 cases caused all health services except emergency procedures to be suspended (8). This study was conducted in a level 1 trauma referral center that also provided intensive COVID-19 services throughout the COVID-19 pandemic. The aim of this study was to compare emergency orthopedic trauma admissions between the pre- and pandemic periods and to detect changes in orthopedic trauma epidemiology. We hypothesized that restrictions during the pandemic period would change trauma exposure and injury mechanisms and differentiate orthopedic trauma epidemiology.

METHODS

Study Design and Level of Evidence

This study employed a retrospective cohort study design, classified as level 3 evidence according to established criteria.

This retrospective cross-sectional study was conducted between March 2019 and March 2021 after the approval of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2021-06-44, protocol code: 2021/168, date: 15.03.2021). The study was registered at clinicaltrials.gov (ID: NCT06237023).

The study was conducted with reference to the date of March 10, 2020, when the first case of COVID-19 was observed in our country. Admissions within the same cross-sectional time period were included in the study when creating the groups. A total of 40,700 patients admitted within 1 year between March 2019 and March 2020 constituted the pre-pandemic group and 16,935 patients admitted between March 2020 and March 2021 constituted the pandemic group. In the study, 57,635 patients who were admitted to the emergency department and the emergency orthopedics department within a 2-year period were examined. Demographic characteristics of the patients, such as age and gender, were recorded. In addition, the injury mechanisms of the patients, diagnosis, injured extremity or anatomical region, broken bone, fracture classification, multitrauma rates [injury severity score (ISS) score ≥15], trauma-related complications, hospitalization days, and treatment modalities were examined. The effects of the pandemic on these data were analyzed by comparing them with the pre-pandemic period.

Statistical Analysis

Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used for data evaluation. The conformity of the quantitative data to the normal distribution was tested using the Shapiro-Wilk test and graphical evaluations. Mann-Whitney U test was used to compare two independent and non-normal distributive variables. The Pearson chi-square test was used to compare qualitative data. Significance was evaluated at the $p<0.05$ level. NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis.

RESULTS

The demographic characteristics of the patients are presented in Table 1. Adult patients, male gender, soft tissue injury, extremity trauma, simple fall, and conservative treatment showed proportional dominance. In the pre-pandemic period, the mean age of the patients was younger, and the distributions of pediatric/adolescent patients and female patients were higher compared with the pandemic period ($p=0.001$, $p=0.001$, and $p=0.001$;

Table 1. Demographic characteristics of the patients

		n	%
Age (years)	Min-max (median)	0-102 (24)	
	Mean ± SD	28.15±19.49	
	Child/adolescent	17,586	30.5
	Adult	40,049	69.5
Gender	Male	32,524	56.4
	Female	25,111	43.6
Injury type	Soft tissue injury	34,828	60.4
	Fracture	20,786	36.1
	Dislocation	1977	3.4
	Fracture dislocation	44	0.1
Fractured bone (n=20,830)	Clavicula	452	2.2
	Humerus	40	0.2
	Radius/Ulna	1610	7.7
	Carpal/Metacarpal	4581	22
	Hand phalanx	2272	10.9
	Vertebra	3326	16
	Pelvic bones	53	0.3
	Femur	117	0.6
	Patella	903	4.3
	Tibia/Fibula	115	0.6
	Tarsal/Metatarsal	1893	9.1
	Foot phalanx	2392	11.5
	Scapula	2882	13.8
	Multipl bone fractures	194	0.9
Gustilo Anderson Classification (n=20,830)	Closed	20,314	97.5
	Type 1 open	411	2
	Type 2 open	47	0.2
	Type 3 open	58	0.3
Injury location	Upper extremity	29,546	51.3
	Lower extremity	27,844	48.3
	Pelvis	122	0.2
	Spine	81	0.1
	Multipl location	42	0.1
Trauma mechanism	Motor vehicle accident	927	1.6
	Pedestrian accident	1348	2.3
	Injury at home	3981	6.9
	Occupational injury	2020	3.5
	Fall from height	941	1.6
	Gunshot injury	59	0.1
	Sports/game injury	2268	3.9
	Simple fall	43,181	74.9
	Beating injury	721	1.3
	Penetrating injury	83	0.1
	Others (unknown cause)	2106	3.7
Multitrauma	ISS score ≥15	439	0.7
Treatment	Conservative	55,389	96.1
	Surgery	2246	3.9
Surgical technique (n=2246)	CRIF	1142	50.8
	ORIF	953	42.5
	Soft tissue surgery	151	6.7
ASA score (n=2246)	I	554	24.7
	II	1001	44.5
	III	691	30.8
Hospitalization (days) (n=2246)	Min-max (median)	1-38 (4)	-
	Mean ± SD	5.10±4.08	-
Trauma releated complications	No	57490	99.7
	Yes	145	0.3

ISS: Injury severity score, ASA: American Society of Anesthesiologists, SD: Standard deviation, min-max: Minimum-maximum, CRIF: Close reduction and internal fixation, ORIF: Open reduction and internal fixation

respectively) (Table 2). Fractures and dislocations were more frequent in the pandemic period, whereas soft tissue injuries were more common in the pre-pandemic period (p=0.001). A statistically significant difference was found between the pre-pandemic and pandemic periods in terms of injury characteristics such as fractured bone, fracture classification, injury location, trauma mechanism, and multitrauma rates (p=0.001). It is noteworthy that accidents at home increased and occupational accidents decreased during the pandemic period (p=0.001). The rate of surgical treatment statistically increased during the pandemic period (p=0.001). However, the surgical technique did not differ (p=0.508). The incidence of trauma-related complications increased by two times compared with the pre-pandemic period (0.2% vs. 0.4%), whereas hospitalization was relatively reduced during the pandemic period (p=0.001 and p=0.023; respectively).

DISCUSSION

The most important aspect of the present study is to show the impact of the COVID-19 pandemic on the demographic, diagnosis, and treatment processes in orthopedic trauma admission and daily orthopedic management. Our study showed that all emergency orthopedic admissions decreased by 58.3% during the pandemic period compared with the 1-year period before the pandemic. Previous studies comparing the pandemic period with the pre-pandemic period showed a similar decrease in emergency orthopedic admissions (2,9-11). The reduced admissions can be explained by a decrease in social mobility caused by strict lockdown precautions taken by governments. It is also

Table 2. Comparison of the demographics, trauma features and the treatment modality of the patients in the pre-pandemic period and the pandemic period

		Pre-pandemic (n=40700)	Pandemic (n=16935)	p-value
		n (%)	n (%)	
Age (years)	Min-max (median)	0-102 (23)	0-101 (26)	[a]**0.001****
	Mean ± SD	27.72±19.36	29.18±19.78	
	Child/adolescent	12,871 (31.6)	4715 (27.8)	[b]**0.001****
	Adult	27,829 (68.4)	12,220 (72.2)	
Gender	Male	22,705 (55.8)	9819 (58.0)	[b]**0.001****
	Female	17,995 (44.2)	7116 (42.0)	
Injury type	Soft tissue injury	26,085 (64.0)	8743 (51.6)	[b]**0.001****
	Fracture	13,342 (32.8)	7444 (44.0)	
	Dislocation	1245 (3.1)	732 (4.3)	
	Fracture dislocation	28 (0.1)	16 (0.1)	
Fractured bone (n=20,830)	Clavicula	268 (2.0)	184 (2.5)	[b]**0.001****
	Humerus	1028 (7.7)	582 (7.8)	
	Radius/Ulna	2763 (20.7)	1818 (24.4)	
	Carpal/Metacarpal	1459 (10.9)	813 (10.9)	
	Hand phalanx	2367 (17.7)	959 (12.9)	
	Vertebra	31 (0.2)	22 (0.3)	
	Pelvic bones	97 (0.7)	20 (0.3)	
	Femur	500 (3.7)	403 (5.4)	
	Patella	84 (0.6)	31 (0.4)	
	Tibia/Fibula	1182 (8.8)	711 (9.5)	
	Tarsal/Metatarsal	1548 (11.6)	844 (11.3)	
	Foot phalanx	1903 (14.2)	979 (13.1)	
	Scapula	23 (0.2)	17 (0.2)	
	Multipl bone fractures	117 (0.9)	77 (1.0)	
Gustilo Anderson Classification (n=20,830)	Closed	13,077 (97.8)	7237 (97.0)	[b]**0.001****
	Type 1 open	223 (1.7)	188 (2.5)	
	Type 2 open	34 (0.3)	13 (0.2)	
	Type 3 open	36 (0.3)	22 (0.3)	
Injury location	Upper extremity	20,637 (50.7)	8909 (52.6)	[b]**0.001****
	Lower extremity	19,898 (48.9)	7946 (46.9)	
	Pelvis	100 (0.2)	22 (0.1)	
	Spine	37 (0.1)	44 (0.3)	
	Multipl location	28 (0.1)	14 (0.1)	
Trauma mechanism	Motor vehicle accident	595 (1.5)	332 (2.0)	[b]**0.001****
	Pedestrian accident	900 (2.2)	448 (2.6)	
	Injury at home	2492 (6.1)	1489 (8.8)	
	Occupational injury	1612 (4.0)	408 (2.4)	
	Fall from height	647 (1.6)	294 (1.7)	
	Gunshot injury	34 (0.1)	25 (0.1)	
	Sports/game injury	1599 (3.9)	669 (4.0)	
	Simple fall	30,463 (74.8)	12,718 (75.1)	
	Beating injury	517 (1.3)	204 (1.2)	
	Penetrating injury	32 (0.1)	51 (0.3)	
	Others (unknown cause)	1809 (4.4)	297 (1.8)	

Table 2. Continued

		Pre-pandemic (n=40700)	Pandemic (n=16935)	p-value
		n (%)	n (%)	
Multitrauma	ISS score ≥15	196 (0.4%)	243 (%1.4)	[b]**0.001****
Treatment	Conservative	39,367 (96.7)	16,022 (94.6)	[b]**0.001****
	Surgery	1333 (3.3)	913 (5.4)	
Surgical technique (n=2246)	CRIF	679 (50.9)	463 (50.7)	[b]**0.508**
	ORIF	558 (41.9)	395 (43.3)	
	Soft tissue surgery	96 (7.2)	55 (6.0)	
ASA score (n=2246)	I	323 (24.2)	231 (25.3)	[b]**0.440**
	II	609 (45.7)	392 (42.9)	
	III	401 (30.1)	290 (31.8)	
Hospitalization (days) (n=2246)	Min-max (median)	1-22 (4)	1-38 (3)	[a]**0.023***
	Mean ± SD	5.23±4.00	4.91±4.19	
Trauma releated complication	No	40,631 (99.8)	16,859 (99.6)	[b]**0.001****
	Yes	69 (0.2)	76 (0.4)	

ISS: Injury severity score, ASA: American Society of Anesthesiologists, SD: Standard deviation, min-max: Minimum-maximum, CRIF: Close reduction and internal fixation, ORIF: Open reduction and internal fixation
[a]Mann-Whitney U Test, [b]Pearson chi-square test, *p<0.05, **p<0.01

a fact that people's fear of being affected by the pandemic and being infected with COVID-19 is effective in reducing hospital admissions, except for emergencies (12).

In the comparison of the number of child/adolescent and adult admissions, there was a significant decrease in the total number of admissions in both groups during the pandemic period compared with the previous year. On the other hand, an increased rate of adult admission and a decreased rate of child/adolescent admission were noteworthy in this study. Several studies have similarly shown that the average age of fractures was higher during the pandemic period compared with previous periods and that there was a decrease in pediatric trauma admissions (13,14). The closure of nurseries and schools during the isolation period, the adoption of distance education, and the partial continuation of workplaces with distance rules may explain why child/adolescent emergency admissions decreased more than adults. In addition, the fact that fragility fractures, which concern the adult age group and especially occur at home, are not affected by social mobility may have contributed to the increased emergency admission rates in adults (15). Some authors have reported that the pandemic had no effect on the male-female patient ratio (16,17) while others have reported an increase in the rate of female admissions compared with males (18). The present study reported a 2.2% decrease in female patients during the pandemic period compared with the pre-pandemic period and an increase in the ratio of male to female patients. Similar to our study, several studies have reported a decrease in the rate of female patient admissions and an increase in the ratio of male to female patients (9,19-22). Due to the closure of nurseries in our country, official permission was given to women with young children and pregnant women who are sensitive to COVID-19, especially to take care of their children. These precautions explain the decrease in trauma exposure and the number of emergency admissions among females.

Kalem et al. (19) reported that soft tissue traumas decreased and the percentage of fractures increased during the pandemic period. In our study, admissions due to fractures increased by 11.2% and soft tissue lesions decreased during the pandemic period. There was no significant change in the dislocation and fracture-dislocation rates. The decrease in soft tissue trauma rates can be explained by the efforts of patients with simple trauma to cope with their problems themselves and perhaps by applying to private hospitals, which are relatively less busy. Vatsya et al. (23) reported that forearm and wrist fractures were the most common during the pandemic period. The largest proportion of admissions during both the pre-pandemic and pandemic periods were for radius/ulna fractures in this study. Radius/ulna fractures were followed by hand phalanx, tarsal/metatarsal, and foot phalanx fractures. An increase in femur and tibia/fibula fractures was detected in the lower extremities (0.7% and 1.7% respectively). The trauma area and broken bone consisted of upper extremity and radius/ulna fractures in both pre-pandemic and pandemic periods, similar to the literature (19).

In this study, the most common trauma mechanism was simple falls. It was observed that strict isolation measures increased domestic injury rates and flexible working hours reduced work accidents. Our data regarding the mechanism of trauma are similar to the literature (3,9,14). Several authors mentioned that traffic accidents and related multitrauma rates have decreased (1,3,9,19,23). Reduced social mobility will generally ensure a decrease in traffic accidents, multitrauma rates, trauma-related complication rates, and open fracture rates. Interestingly, there was a statistically significant increase in the application rates for pedestrian and motor vehicle accidents in the present study. Similarly, we found a statistically significant increase in trauma-related complication rates, multitrauma (ISS score ≥15), and open fracture rates. Previous studies investigating treatment methods have shown that the tendency toward conservative treatment increased during the pandemic period (24). However, trauma-related complication rates were twice as high as those in the pre-pandemic period, and a significant increase in surgical treatment rates was found in our study. Considering that these parameters (multitrauma, trauma-related complications, open fractures and the need for surgical treatment) are directly related to the severity of trauma, the main reason for the increase in these parameters is that our hospital not only provided COVID-19 healthcare services but also actively accepted trauma. It is noteworthy that similar outcomes have been reported in the literature in such studies conducted in primary trauma referral centers (20,25-28). In addition, we examined the changes in the length of stay of inpatients and found that our findings were in line with the literature and there was no significant difference (29,30).

This study has limitations, such as being a single-center and retrospective design. In addition, our study shows the epidemiology of the data, and we did not present any data on patient follow-up or outcomes. Studies in the literature generally investigate the effects of the pandemic on trauma epidemiology by comparing short periods. In our study, comparing the pandemic period with the 1-year period before the pandemic minimized the effect of seasonal changes on trauma admissions. This provides more reliable data on the isolated impact of the pandemic on the etiology of orthopedic trauma. However, because the center where our study was conducted is a primary trauma referral center hospital in the most populous city of the country, the high number of patients included in the study and the high number of trauma admissions make our study strong. However, studies involving more centers and perhaps longer-term analyses are needed to fully understand the impact of the pandemic on orthopedic trauma epidemiology.

CONCLUSION

In conclusion, considering the epidemiology of orthopedic trauma, being able to estimate the trauma burden and optimizing resource use and allocation are essential for maintaining safe and effective treatment services for patients in extraordinary situations such as the COVID-19 pandemic, which can cause serious disruptions in the healthcare system. The present study will guide clinicians to better understand the burden of orthopedic trauma and to be prepared for extraordinary situations such as the COVID-19 pandemic that need to be managed and to optimize resource allocation and use.

ETHICS

Ethics Committee Approval: University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approval was received from (decision no: 2021-06-44, protocol code: 2021/168, date: 15.03.2021).

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

Authorship Contributions

Concept: V.Ö., A.D., Design: V.Ö., A.D., Data Collection or Processing: B.B.Ç., A.C.K., Analysis or Interpretation: V.Ö., B.B.Ç., A.C.K., Literature Search: V.Ö., B.B.Ç., M.Ç., Writing: V.Ö., M.Ç., A.D.

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

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

REFERENCES

1. Blum P, Putzer D, Liebensteiner MC, Dammerer D. Impact of the Covid-19 Pandemic on Orthopaedic and Trauma Surgery - A Systematic Review of the Current Literature. In Vivo 2021;35:1337-43.
2. Miranda I, Sangüesa-Nebot MJ, González A, Doménech J. Impact of strict population confinement on fracture incidence during the COVID-19 pandemic. Experience from a public Health Care Department in Spain. J Orthop Sci 2022;27:677-80.
3. Nuñez JH, Sallent A, Lakhani K, Guerra-Farfan E, Vidal N, Ekhtiari S, et al. Impact of the COVID-19 Pandemic on an Emergency Traumatology Service: Experience at a Tertiary Trauma Centre in Spain. Injury 2020;51:1414-8.
4. Ruggieri P, Trovarelli G, Angelini A, Pala E, Berizzi A, Donato D. COVID-19 strategy in organizing and planning orthopedic surgery in a major orthopedic referral center in an area of Italy severely affected by the pandemic: experience of the Department of Orthopedics, University of Padova. J Orthop Surg Res 2020;15:279.

5. Maniscalco P, Ciatti C, Gattoni S, Quattrini F, Puma Pagliarello C, Patane' AC, et al. Proximal humerus fractures in COVID-19 lockdown: the experience of three orthopedics and traumatology departments in the first ten weeks of the Italian epidemic. Acta Biomed 2021;92:e2021104.
6. Soni A, Garg SK, Gupta R, Gupta P, Kansay R, Singhal A. Epidemiologic characteristics and pre-hospital care of traumatic injuries during the COVID-19 pandemic in an emerging and developing country: A single tertiary centre experience. J Clin Orthop Trauma 2021;23:101654.
7. Haffer H, Schömig F, Rickert M, Randau T, Raschke M, Wirtz D, et al. Impact of the COVID-19 Pandemic on Orthopaedic and Trauma Surgery in University Hospitals in Germany: Results of a Nationwide Survey. J Bone Joint Surg Am 2020;102:e78.
8. Obamiro E, Trivedi R, Ahmed N. Changes in trends of orthopedic services due to the COVID-19 pandemic: A review. World J Orthop 2022;13:955-68.
9. Bhat AK, Kamath KS. Comparative study of orthopaedic trauma pattern in covid lockdown versus non-covid period in a tertiary care centre. J Orthop 2021;23:1-7.
10. Farrell S, Schaeffer EK, Mulpuri K. Recommendations for the care of pediatric orthopedic patients during the COVID pandemic. J Am Acad Orthop Surg 2020;28:e477-e86.
11. Migliorini F, Weber CD, Pappalardo G, Schenker H, Hofmann UK, Eschweiler J, et al. Orthopaedic, trauma surgery, and Covid-2019 pandemic: clinical panorama and future prospective in Europe. Eur J Trauma Emerg Surg 2022;48:4385-402.
12. Harper CA, Satchell LP, Fido D, Latzman RD. Functional fear predicts public health compliance in the COVID-19 pandemic. Int J Ment Health Addict 2021;19:1875-88.
13. Bolzinger M, Lopin G, Accadbled F, Sales de Gauzy J, Compagnon R. Pediatric traumatology in "green zone" during Covid-19 lockdown: a single-center study. Orthop Traumatol Surg Res 2023;109:102946.
14. Zagra L, Faraldi M, Pregliasco F, Vinci A, Lombardi G, Ottaiano I, et al. Changes of clinical activities in an orthopaedic institute in North Italy during the spread of COVID-19 pandemic: a seven-week observational analysis. Int Orthop 2020;44:1591-8.
15. Keegan TH, Kelsey JL, King AC, Quesenberry CP Jr, Sidney S. Characteristics of fallers who fracture at the foot , distal forearm , proximal humerus, pelvis, and shaft of the tibia/fibula compared with fallers who do not fracture. Am J Epidemiol 2004;159:192-203.
16. Bedard NA, Elkins JM, Brown TS. Effect of COVID-19 on Hip and Knee Arthroplasty Surgical Volume in the United States. J Arthroplasty 2020;35(7S):S45-S8.
17. Liebensteiner MC, Khosravi I, Hirschmann MT, Heuberer PR; Board of the AGA-Society of Arthroscopy and Joint-Surgery; Thaler M. Massive cutback in orthopaedic healthcare services due to the COVID-19 pandemic. Knee Surg Sports Traumatol Arthrosc 2020;28:1705-11.
18. Klepacki K, Tomczyk Ł, Miękisiak G, Morasiewicz P. The Effect of the Covid-19 Pandemic on the Epidemiology of Ankle Joint Injuries in Adults and Children. Ortop Traumatol Rehabil 2022;24:363-73.
19. Kalem M, Kocaoğlu H, Merter A, Karaca MO, Özbek EA, Kınık HH. Effects of COVID-19 pandemic curfew on orthopedic trauma in a tertiary care hospital in Turkey. Acta Orthop Traumatol Turc 2021;55:191-5.
20. Kamacı S, Göker B, Çağlar Ö, Atilla B, Tokgözoğlu AM. The effect of the COVID-19 pandemic on orthopedic surgeries in a tertiary referral center. Jt Dis Relat Surg 2021;32:333-9.
21. Markiewitz ND, Garcia-Munoz J, Lilley BM, Oduwole S, Shah AS, Williams BA. Epidemiologic Changes in Pediatric Fractures Presenting to Emergency Departments During the COVID-19 Pandemic. J Pediatr Orthop 2022;42:e815-e20.
22. Lapsa J, Bukola Badaki O, Xu A, Eaton C, Lee RJ, Ryan L. The COVID-19 Pandemic: Effects on Pediatric Fracture Patterns in the Emergency Department and Subspecialty Follow-up Care. J Pediatr Orthop 2022;42:582-8.
23. Vatsya P, Garika SS, Mittal S, Trikha V, Sharma V, Malhotra R. Lockdown imposition due to COVID-19 and its effect on orthopedic emergency department in level 1 trauma center in South Asia. J Clin Orthop Trauma 2022;28:101826.
24. Jiang SH, Davison-Kerwood M, Gonzalez MH. Increased Rate of Fracture Injuries Associated With Alternative Modes of Transportation During COVID-19. J Am Acad Orthop Surg Glob Res Rev 2022;6:e22.00147.
25. Alencar Neto JB, Oliveira ED, Branco MCC, Ozório RG, Sousa AAF, Cavalcante MLC, et al. The Impact Of COVID-19 On The Epidemiological Profile Of Fractures. Acta Ortop Bras 2022;30:e252472.
26. Pintado JF, Gibaja W, Vallejos RA, Rosas W, Guerra-Farfan E, Nuñez JH. How COVID-19 has affected emergent visits to a Latin-American trauma department: Experience at a Peruvian national trauma referral center. Injury 2020;51:2834-9.
27. Dhillon MS, Kumar D, Saini UC, Bhayana H, Gopinathan NR, Aggarwal S. Changing Pattern of Orthopaedic Trauma Admissions During COVID-19 Pandemic: Experience at a Tertiary Trauma Centre in India. Indian J Orthop 2020;54(Suppl 2):374-9.
28. O'Hagan P, Drummond I, Lin D, Khor KS, Vris A, Jeyaseelan L. Impact of the COVID-19 pandemic on the management of open fractures in a major trauma centre. J Clin Orthop Trauma 2021;21:101509.
29. Stafford AP, Hoskin TL, Hieken TJ, Sanders S, Pruthi S, Boughey J, et al. Lessons learned from the COVID-19 pandemic: Using telemedicine for pre-operative surgical evaluation in breast disease. J Telemed Telecare 2023:1357633X231194377.
30. Shankar DS, Li ZI, Hoberman AR, Blaeser AM, Gonzalez-Lomas G, Youm T. Patient Satisfaction with Postoperative Telemedicine Versus In-Office Visits Following Primary Hip Arthroscopy: A Prospective Observational Study Before and During the COVID-19 Pandemic. Telemed J E Health 2024;30:464-71.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:159-167
DOI: 10.4274/BMJ.galenos.2024.2023.6-3

Research

Women's Health Literacy Levels and Health Beliefs Concerning Cervical Cancer and Pap Smear Test in Türkiye

Türkiye'de Kadınların Sağlık Okuryazarlığı Düzeyleri ile Serviks Kanseri ve Pap Smear Testine İlişkin Sağlık İnançları

Ayşe Dost[1], İrem Nur Özdemir[2]

[1]Bezmialem Vakıf University Faculty of Health Sciences, Department of Nursing, İstanbul, Türkiye

[2]University of Health Sciences Türkiye, Bakirköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Education and Research & Development, İstanbul, Türkiye

ABSTRACT

Objective: This study examined the relationship between women's health literacy levels, their health belief levels concerning cervical cancer, and the Pap smear test.

Methods: This descriptive and relationship-seeking study was conducted with 519 women who were selected using the purposive sampling method and met the inclusion criteria. Data were collected using a questionnaire by the researchers, the Turkey Health Literacy Survey (THLS-32) and the Health Belief Model Scale for Cervical Cancer and the Pap Smear Test (HBM-SCCPST).

Results: The mean THLS-32 score of the women was 32.08±11.85 and 30.2% had an insufficient level of health literacy. Women's education, occupation, economic status, knowledge of the Pap smear, and willingness to be vaccinated against the human papillomavirus were found to be factors affecting their health literacy ($p<0.05$). The mean subscale scores in the HBM-SCCPST were determined to be 30.83±8.46 for Pap smear benefits, 32.70±11.41 for barriers, 22.16±6.06 for cervical cancer-seriousness, 7.83±2.40 for cervical cancer-susceptibility, 9.15±2.86 for cervical cancer health motivation. The women's health literacy levels had a weak positive correlation with their mean Pap smear benefits subscale score ($r=0.275$), weak negative relationship with their mean barriers subscale score ($r=-0.212$) ($p=0.000$).

Conclusion: In this study, it was observed that as the health literacy levels of the women increased, there was a decrease in their barrier perception and an increase in their benefit perception concerning the Pap smear test. The results suggest that women's health literacy levels are moderate, and there is a need for interventions to increase their health literacy.

Keywords: Pap smear test, cervical cancer, health literacy, beliefs

ÖZ

Amaç: Kadınların sağlık okuryazarlığı düzeyleri ve serviks kanseri ve Pap smear testine ilişkin sağlık inanç düzeyleri arasındaki ilişkinin incelenmesidir.

Gereç ve Yöntem: Tanımlayıcı ve ilişki arayıcı tipte olan bu araştırma amaçsal örnekleme yöntemi ile seçilen ve dahil edilme kriterlerine uyan 519 kadın ile gerçekleştirildi. Veriler araştırmacılar tarafından hazırlanan anket formu, Serviks Kanseri ve Pap Smear Testi Sağlık İnanç Modeli Ölçeği (SKPST-SİMÖ) ve Türkiye Sağlık Okuryazarlığı Ölçeği (TSOY-32) kullanılarak toplandı.

Bulgular: Kadınların TSOY-32 puan ortalamaları 32,08±11,85 olup, %30,2'sinin sağlık okuryazarlığı "yetersiz" düzeydedir. Kadınların eğitim düzeyi, mesleği, ekonomik durum, sigara kullanımı, Pap smear testini bilme ve insan papillom virüsü aşısı olmak isteme durumu sağlık okuryazarlığını etkileyen faktörler olarak bulunmuştur ($p<0,05$). SKPST-SİMÖ Pap smear yarar ve motivasyon alt boyutundan 30,83±8,46 puan, "Pap smear engeller" alt boyutundan 32,70±11,41 puan, "serviks kanseri önemseme/ciddiyet" alt boyutundan 22,16±6,06 puan, "serviks kanseri duyarlılık" alt boyutundan 7,83±2,40 puan ve "serviks kanseri sağlık motivasyonu" alt boyutundan 9,15±2,86 puan aldıkları saptandı. Kadınların, sağlık okuryazarlık düzeyi ile "Pap smear yarar ve motivasyonu" alt boyutu puan ortalamaları arasında pozitif yönde zayıf bir ilişki ($r=0,275$) ve "Pap smear engeller" alt boyutu puan ortalamaları arasında ise negatif yönde zayıf bir ilişki ($r=-0,212$) olduğu görülmektedir ($p=0,000$).

Sonuç: Çalışmada kadınların sağlık okuryazarlığı düzeyi arttıkça Pap smear testi engel algısının azaldığı, yarar algısının ise arttığı görülmüştür. Sonuçlar, kadınların sağlık okuryazarlığının orta düzeyde olduğunu göstermekte olup, sağlık okuryazarlığını artıracak müdahalelere gereksinim bulunmaktadır.

Anahtar Kelimeler: Pap smear testi, rahim ağzı kanseri, sağlık okuryazarlığı, inançlar

Address for Correspondence: İrem Nur Özdemir, University of Health Sciences Türkiye, Bakirköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Education and Research & Development, İstanbul, Türkiye
Phone: +90 212 414 75 56 E-mail: iremozdemir92@gmail.com ORCID ID: orcid.org/0000-0002-1122-0514

Cite as: Dost A, Özdemir İN. Women's Health Literacy Levels and Health Beliefs Concerning Cervical Cancer and Pap Smear Test in Türkiye. Med J Bakirkoy 2024;20:159-167

Received: 08.08.2023
Accepted: 12.02.2024

INTRODUCTION

Health literacy allows individuals to access accurate information, participate in their own health services, improve their health, and build individual and community resilience by addressing health inequalities (1). Individuals with sufficient health literacy can take responsibility for their health and community health (2). This concept has gained even more importance during the most recent pandemic of coronavirus disease (3). Individuals with low health literacy cannot effectively distinguish between facts and fiction and may allow unreliable information to influence their actions and quality of life (4). Unfortunately, this harms not only the individual but also society as a whole. This situation can be further worsened by myths about diseases and unclear and incomprehensible health information spread on social media, and inaccurate information in society can negatively affect the psychological health and quality of life of the public (1,4,5).

Health literacy affects women's health in many ways. Improving women's health is particularly important because of its effects on family and community health (6). Having a high level of health literacy is an important factor for women to protect and promote their health throughout their life cycles, and it also affects newborn and child health (6,7). Increases a woman's capacity to take responsibility for her own health, as well as the health of her family, and affects her and her family's ability to seek solutions for their health problems (8). Health literacy is also considered an important focus, especially for women's reproductive health (9). It has been reported that women with a high level of health literacy have a healthy pregnancy and postpartum period, feed their infants only breast milk for the first 6 months, and participate in gynecological cancer screening at favorable levels. Studies have also shown that individuals with a high level of health literacy are more conscious and have a higher quality of life (4,5). However, as levels of health literacy decline, difficulties in participating in medical decisions, following medical advice, and attending follow-up appointments have been identified. It has been reported that adults with limited health literacy receive less information from materials on disease prevention and control and have lower rates of participation in screenings (10,11).

Cervical cancer is an important community health problem worldwide (12). Although cervical cancer is included in screening programs in Türkiye, as in many other parts of the world, and can be diagnosed early, deaths due to this cancer still occur at a high rate. Cervical cancer is globally the fourth most common cancer among women, with an estimated 604,000 new cases and 342,000 deaths in 2020 (12).

According to GLOBOCAN 2020 data, while 604,127 new cervical cancer cases were detected across the world, the number of deaths caused by cervical cancer was found to be more than 340,000 (13). There are also significant differences in the incidence of cervical cancer between countries with the highest and lowest human development rates (14,15).

Women's health in Türkiye is deeply linked to the dynamics of health systems and society. Women's health literacy level is critical, especially in terms of the early diagnosis of preventable diseases such as cervical cancer and the role it plays in healthy living. It is thought that this research will help understand the underlying reasons for the low cervical screening participation of women in Türkiye. In Türkiye, the relationship between women's health literacy level and preventive methods such as cervical cancer and Pap smear test is not well understood. In this context, one of the deficiencies in the literature is that women's health literacy level in Türkiye has a significant impact on their level of knowledge about cervical cancer and their access to preventive tests such as Pap smear. This is because its effects have not been studied in detail. This study was conducted to fill the gap in the field of women's health in Türkiye, to understand the relationship between health literacy levels and cervical cancer and the Pap smear test, and to contribute to shaping health policies in this context. Therefore, this study aimed to determine the relationship between women's health literacy levels and their health belief levels concerning cervical cancer and the Pap smear test. The research questions were as follows:

- What are women's health literacy levels and health belief levels concerning cervical cancer and the Pap smear test?
- Is there a significant relationship between women's health literacy levels and their health belief levels concerning cervical cancer and the Pap smear test?
- What are the factors associated with women's health literacy levels and health belief levels concerning cervical cancer and the Pap smear test?

METHODS

Research Design and Sample

This research was conducted as a descriptive-relationship-seeking study, and the population consisted of 246,739 individuals who presented to the outpatient clinics of a training and research hospital located on the European side of Istanbul from December 27, 2021, through January 30, 2022. The sample size was determined as a minimum of

384 individuals, considering the sample size table, at 95% confidence and ±0.05 margin of error. The study sample comprised 519 individuals who were selected using the convince sampling method and met the inclusion criteria. The inclusion criteria were being a woman and volunteering to participate in the study.

Data Collection Tools

Descriptive characteristics form: This form was prepared by the researchers from the literature and consisted of 16 questions related to age, education level, marital status, occupation, age at marriage, age at first birth, the status of attending gynecological examinations, reasons for not attending gynecological examinations, place of residence, economic status, smoking status, presence of cervical cancer in the family, status of having a Pap smear test, and knowledge of and willingness to receive human papilloma virus (HPV) vaccination (16-19).

Turkey Health Literacy Survey (THLS-32): This scale was developed by Okyay et al. (20) in 2016 within the scope of the European Health Literacy Survey study. It consists of 32 Likert-type questions with the options of "very easy", "easy", "difficult", "very difficult", and "don't know". The lowest score that can be obtained from the scale is 0, and the highest score is 50. As the score increases, the level of health literacy of the individuals also increases. According to the score obtained, health literacy is interpreted at four levels: insufficient, 0-25 points; problematic-limited, >25-33 points; sufficient, >33-42 points; and excellent, >42-50 points.

The conceptual framework of THLS-32 includes two health-related dimensions ("treatment and service" and "disease prevention and health promotion") and four information-gathering processes ("access", "understanding", "evaluation", and "use/application") related to health-related decision-making and practices. In this study, the overall internal consistency coefficient of the scale was determined to be 0.957. The Cronbach alpha coefficients were found to be 0.915 for the treatment and service subscale and 0.950 for the disease prevention and health promotion subscale.

Health Belief Model Scale for Cervical Cancer and the Pap Smear Test (HBM-SCCPST): The Health Belief Model Scale was developed by Champion in 1997 to evaluate individuals' beliefs about breast cancer. In 2011, this scale was adapted and standardized by Guvenc et al. (21) to evaluate the beliefs about cervical cancer. Because of the standardization study, five subscales were identified: susceptibility, seriousness, benefits, barriers, and health motivation. There are three items in the susceptibility subscale, seven in the seriousness subscale, eight in the benefits subscale, 14 in the barriers subscale, and three in the health motivation subscale. In the evaluation of the scale, a 5-point Likert-type scale ranging from 1 to 5 - "strongly disagree" (1), "disagree" (2), "undecided" (3), "agree" (4), "completely agree" (5) method was used. Each dimension of the scale is evaluated separately and is not combined into a single total score. For each individual, scores equal to the number of subscales are obtained. Higher scores indicate increased susceptibility, seriousness, and health motivation; It indicates that the benefits are perceived as high for benefit perception and the barriers are perceived as high for barriers perception.

Data Collection

Study data were collected through face-to-face interviews with women who presented to the outpatient clinics of a training and research hospital on the European side of İstanbul between December 27, 2021, and January 30, 2022 and volunteered to participate in the research. Data collection took 20-25 minutes. Whether all forms were completed was checked during the data collection phase, and it was ensured that no sample loss occurred due to missing data.

Ethical Considerations: Approval was obtained from the Non-invasive Clinical Research Ethics Committee of İstanbul Medipol University on November 25, 2021 (decision no: 1151). Written institutional permission was obtained from the hospital management where the study was planned. All women who participated in the study provided informed consent.

Statistical Analysis

Statistical analyses were performed using IBM SPSS for Windows, version 22.0. Descriptive tests of frequency, percentage, mean, and standard deviation were employed. The distribution of numeric variables was tested using the Kolmogorov-Smirnov test, and it was determined that the data did not have a normal distribution ($p=0.00$). Therefore, the differences between the variables related to individual characteristics and the questionnaire scores were analyzed using the Mann-Whitney U and Kruskal-Wallis tests. To determine the association between the scores of the THLS-32 and the HBM-SCCPST, a coefficient analysis was undertaken. Statistical significance was considered at $p<0.05$.

RESULTS

The mean age of the women was 31.33±10.35 years, 31.8% (n=165) were housewives, and 57.4% (n=298) were married. The mean age at marriage was 23.84±4.56 years,

and the mean age at first birth was 24.94±5.16 years. The remaining sociodemographic data are presented in Table 1. Approximately half (48.4%) of the women stated that they had not undergone a gynecological examination. The reasons for not attending gynecological examinations were having no complaints (48.7%), not considering it necessary (35.6%), not being recommended by any physician (7.3%), fears (5.4%), and feeling ashamed (3%).

It was determined that women with undergraduate and postgraduate degrees, those working as civil servants, those with good economic status, non-smokers, occasional smokers, and women who were willing to be vaccinated against HPV had significantly higher mean THLS-32 scores than the remaining participants (p<0.05) (Tables 1,2).

Table 1. Distribution of the Health Belief Model Scale for Cervical Cancer and the Pap Smear Test and THLS-32 mean ranks according to women's demographic characteristics (n=519)

					Health Belief Model Scale for Cervical Cancer and the Pap Smear Test (HBM-SCCPST)				
				THLS-32	Susceptibility	Seriousness	Benefits	Barriers	Health motivation
Variables		**n**	**%**	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**
Education level	Illiterate	38	7.3	152.65	243.46	217.56	192.55	185.23	112.85
	Literate	20	3.9	162.46	176.43	177.39	188.54	196.54	224.65
	Primary school	81	15.6	162.50	206.32	217.37	181.55	161.50	189.54
	Middle school	30	5.8	172.56	209.63	163.10	231.80	159.50	132.80
	High school	135	26	131.83	173.39	201.81	147.70	175.55	184.59
	Undergraduate	202	38.9	187.13	169.40	185.16	331.32	188.21	302.80
	Postgraduate	13	2.5	195.67	207.23	226.42	201.32	160.53	194.43
	KW/p			14.475/**0.002**	10.838/0.055	6.670/0.154	26.844/**0.000**	12.116/0.0533	13.218/**0.021**
Occupation	Housewife	165	31.8	132.12	216.22	265.94	161.96	146.82	207.69
	Civil servant	126	24.2	203.76	175.39	213.88	216.10	202.92	225.58
	Employed in the private sector	141	27.2	191.73	233.49	165.24	191.43	219.62	192.70
	Retired	4	0.8	192.85	83.00	384.50	326.50	175.00	300.50
	Self-employed	80	15.4	88.00	151.00	135.50	239.50	93.00	80.00
	Other	3	0.6	116.25	194.57	210.58	209.52	204.49	201.01
	KW/p			11.569/**0.041**	13.808/**0.017**	19.182/**0.002**	9.403/0.094	12.132/**0.033**	9.126/0.104
Marital status	Married	298	57.4	205.42	199.84	219.85	192.61	205.02	223.32
	Single	221	42.6	187.24	189.83	207.24	224.29	203.18	203.03
	Z/p			-1.579/0.114	-.894/.371	-1.056/.291	-**2.672/0.008**	-0.157/0.875	-1.713/0.087
Place of residence	Province	440	84.8	195.70	192.84	206.60	207.04	195.06	208.32
	District	46	8.9	201.09	165.59	229.69	193.09	243.03	211.99
	Village	33	6.3	187.80	360.50	161.20	252.10	157.00	281.30
	KW/p			0.088/0.957	7.096/**0.029**	1.671/0.434	1.153/0.562	5.992/0.050	1.854/0.396
Economic status	Poor	62	11.9	176.345	202.12	154.28	153.43	181.16	146.89
	Moderate	360	69.4	201.18	187.14	203.86	215.47	213.16	209.43
	Good	97	18.7	241.95	234.39	223.13	228.74	180.95	271.78
	KW/p			6.301/**0.043**	8.318/**0.016**	11.307/**0.004**	10.205/**0.006**	5.254/**0.032**	28.798/**0.000**
Smoking status	Non-smoker	374	72	200.03	185.91	212.81	203.93	198.09	212.05
	Smoker, at least once a day	84	16.2	180.78	219.86	200.96	218.76	212.28	192.72
	Occasionally	38	7.3	258.26	243.07	237.86	239.74	180.00	208.62
	Ex-smoker	23	4.4	58.00	297.50	405.90	399.00	77.60	236.05
	KW/p			21.433/**0.000**	17.055/**0.001**	14.413/**0.002**	15.508/**0.001**	8.816/**0.032**	2.932/**0.002**

*P<0.05. THLS-32: Turkey Health Literacy Survey, SD: Standard deviation, Z: Mann-Whitney U test statistic, KW: Kruskal-Wallis test statistic

Table 2. Distribution of the Health Belief Model Scale for Cervical Cancer and the Pap Smear Test and THLS-32 mean ranks according to the women's other descriptive characteristics (n=519)

				THLS-32	Health Belief Model Scale for Cervical Cancer and the Pap Smear Test (HBM-SCCPST)				
					Susceptibility	Seriousness	Benefits	Barriers	Health motivation
Variables		**n**	**%**	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**	**Mean rank**
Cervical cancer in the family	Present	27	5.2	159.27	288.92	248.31	270.85	119.73	268.52
	Absent	492	94.8	198.40	188.30	207.67	204.14	205.66	207.52
	Z/p			-1.645/0.100	-3.818/**0.000**	-1.599/0.110	-2.653/0.128	-3.534/**0.000**	-2.409/**0.016**
Pap smear test history	Present	53	10.2	139.70	188.09	157.53	174.73	162.14	160.18
	Absent	466	89.8	167.02	147.57	172.11	169.82	168.38	178.57
	Z/p			-1.754/0.079	-2.680/0.127	-0.965/0.335	-0.319/0.750	-0.411/0.681	-1.190/0.234
Has anyone heard of HPV before?	Yes	173	33.3	193.61	190.00	199.42	205.59	195.77	200.59
	No	346	66.7	183.76	178.06	210.25	188.71	187.43	212.25
	Z/p			-0.771/0.441	-0.993/0.321	-0.843/0.399	-1.301/0.193	-0.654/0.513	-0.919/0.358
Has anyone heard of HPV vaccine before?	Yes	84	16.2	190.41	188.29	185.51	217.70	182.84	213.48
	No	435	83.8	187.77	182.51	215.72	189.07	206.23	198.53
	Z/p			-0.235/0.814	-0.525/0.599	-2.597/**0.009**	-2.463/**0.014**	-0.032/**0.042**	-1.281/0.200
Willing to undergo HPV vaccination?	Yes	221	42.6	131.43	123.99	131.30	131.99	123.26	136.55
	No	298	57.4	98.36	104.35	123.69	127.94	126.29	130.43
	Z/p			**-3.118/0.002**	**-2.015/0.044**	-0.697/0.486	-0.376/0.707	-0.286/0.775	-0.566/0.571

*P<0.05. THLS-32: Turkey Health Literacy Survey, SD: Standard deviation, , HPV: Human papillomavirus, Z: Mann-Whitney U test statistic, KW: Kruskal-Wallis test statistic

The Pap smear test benefit perception was higher among single women than among married women. The Pap smear test benefit perception and health motivation scores of undergraduate women were higher than those of the remaining participants (p<0.05). The Pap smear test benefit and cervical cancer sensitivity scores of the women working in the private sector and the cervical cancer seriousness score of the retired women were higher than those of the remaining participants (p<0.05). Economic level and smoking status were determined to be factors affecting all subscale scores in the HBM-SCCPST (p<0.05). Women with a good economic status and ex-smokers had significantly higher scores in the Pap smear benefits, cervical cancer seriousness, cervical cancer susceptibility, and cervical cancer health motivation subscales than the remaining women, whereas those with a moderate economic status and those who smoked at least once a day had a higher Pap smear barriers subscore (p<0.05) (Table 1).

Of the participants, 5.2% had a family member diagnosed with cervical cancer, 10.2% had undergone a Pap smear test, 33.3% had heard of HPV before, 16.2% had heard of the HPV vaccine, and 57.4% were not willing to be vaccinated against HPV (Table 2).

The cervical cancer susceptibility and cervical cancer health motivation scores were higher among women with a family history of cervical cancer than among the remaining women. Women without a family history of cervical cancer had a higher Pap smear barrier score. Those who had not heard of the HPV vaccine before had higher cervical cancer-seriousness and Pap smear-barrier scores than the remaining women. In contrast, the Pap smear benefit score of the women who had heard of the HPV vaccine was higher than that of the other women (p<0.05). Lastly, the participants who were willing to receive HPV vaccination had a higher cervical cancer susceptibility score than those who were not willing to be vaccinated against HPV (p<0.05) (Table 2).

The health literacy level was determined to be insufficient in 30.2% of the women, limited in 25.7%, sufficient in 18.3%, and excellent in 26%. The mean THLS-32 score was 32.08±11.85. When the subscales of the THLS-32 were examined, the mean scores were found to be 31.93±12.10 for treatment and service, 32.49±12.11 for disease prevention and health promotion, 15.91±6.29 for accessing health-related information, 16.01±6.44 for understanding health-related information, 16.51±6.08 for evaluating health-related information, and 15.85±5.92 for using health-related information.

The women's mean HBM-SCCPST scores according to the subscales were as follows: Pap smear benefits, 30.83±8.46; Pap smear obstructions, 32.70±11.41; cervical cancer

seriousness, 22.16±6.06; cervical cancer susceptibility, 7.83±2.40; and cervical cancer health motivation, 9.15±2.86.

When the relationship between the mean THLS-32 score and the HBM-SCCPST subscale scores was examined, the THLS-32 score had a weak positive correlation with the Pap smear benefit score (r=0.275) and a weak negative correlation with the Pap smear barrier score (r=-0.212) (p=0.000) (Table 3).

DISCUSSION

A sufficient level of health literacy, which is accepted as the key to improving health, ensures that individuals effectively benefit from health services and regularly participate in health screening, as well as increasing productivity at the societal level. The current study examined the relationship between women's health literacy levels and their health beliefs concerning cervical cancer and the Pap smear test. According to the results, the health literacy of the participant women was moderate, and 30.2% had insufficient health literacy. As the level of health literacy increased, there was a decrease in the perception of barriers and an increase in the perception of benefits concerning the Pap smear test. In the literature, it has been determined that individuals with low health literacy have a lower propensity to participate in cancer screening because they have difficulty making the right decision about their health (22). Low health literacy is associated with a decrease in the use of cancer screening methods, delayed diagnosis, difficulty in choosing treatment, and reduced quality of life (23). Low health literacy is one of the greatest obstacles to following screening recommendations because it limits individuals' ability to understand and evaluate cancer screening methods (24). Similarly, the low rate of our participants' use of early diagnosis/screening services is considered to be due to the insufficient and problematic/limited health literacy levels of most participants. In a study by Ducray et al. (25), the tendency to undergo the Pap smear test was found to be significantly higher among individuals who knew about cervical cancer. A study of Asian immigrant women similarly showed that health literacy was associated with Pap smear practice (26). The capacity to acquire and understand health-related information is an important determinant in making health-related decisions. Lack of information is one of the major barriers to participation in screening. Healthcare providers should be aware that women's health literacy may affect their cervical cancer screening attitudes. Therefore, nurses play a crucial role in ensuring that information on cervical cancer is understandable to encourage Pap smear testing.

In this study, it was found that almost half of the women had never undergone a gynecological examination, 70% had never heard of HPV or had a very low awareness of HPV, and half were not willing to receive HPV vaccination. The literature suggests that the absence of a history of gynecological examination is an obstacle to the Pap smear test (27,28). The knowledge level of the women in our study was mostly consistent with other studies (5,29,30). In a study conducted in Nepal, it was found that 53% of women had insufficient knowledge, and another study in Malta reported that participants had moderate knowledge (31,32). Although cervical cancer screening programs are conducted on a national scale, the level of knowledge concerning HPV remains low. In this context, it can be stated that public education on the role of HPV in cervical cancer has been unsuccessful.

Table 3. Relationship between THLS-32 and HBM-SCCPST scores

HBM-SCCPST subscales		THLS Subscales		
		Treatment and service	Disease prevention and health promotion	THLS-32 total
Susceptibility	r	0.082	0.104	0.085
	p	0.122	0.053	0.123
Seriousness	r	0.030	0.041	0.016
	p	0.553	0.415	0.757
Benefits	r	0.217	0.294	0.275
	p	**0.000**	**0.000**	**0.000**
Barriers	r	-0.175	-0.240	-0.212
	p	**0.000**	**0.000**	**0.000**
Health motivation	r	0.001	-0.020	-0.011
	p	0.981	0.689	0.832

*P<.01; THLS-32: Turkey Health Literacy Survey, HBM-SCCPST: Health Belief Model Scale for Cervical Cancer and the Pap Smear Test, r: correlation coefficient

In this study, only 10% of the women had previously undergone a Pap smear test. In a study conducted with Asian immigrant women in South Korea, the rate of those who had previously undergone a Pap smear test was 23.5% (26). The low rate of participation in screening tests indicates that women are still unaware of preventive measures for cervical cancer. In South Korea, women aged 20 years and over are entitled to a free Pap smear test every two years under health insurance (33). In Türkiye, cervical screening is performed every 5 years for women aged 30-65 years (34). A systematic review on this subject found that cervical cancer education doubled screening rates and could be a useful initiative for communities with low health literacy levels (35).

Therefore, women should be made aware of and educated about healthy sexual behavior and cervical cancer screening. We determined that the mean health literacy scores of women with undergraduate and postgraduate degrees were significantly higher than those of the remaining participants. A study by Acharya Pandey and Karmacharya (31) found a significant relationship between adequate knowledge, attitudes, and practices and a higher level of education. It was also noted that literate women had a higher rate of sufficient knowledge. Individuals with higher education levels have higher health literacy, which is also a common finding in the literature. Increasing education is important to increasing the level of health literacy because better-educated individuals are better able to obtain the information necessary to address health problems (36-38). This is related to health literacy facilitating the processes of accessing, understanding, and evaluating health information (39).

Of the participants in this study, 5.2% had a family member diagnosed with cervical cancer, and this group was found to have higher susceptibility and health motivation scores for cervical cancer than the remaining participants. In addition, the perception of barriers was higher among those without a family history of cancer. This finding is supported by Chorley et al. (40), who reported that women with close family members suffering from cancer were more likely to undergo cervical cancer screening. Kim et al. (41) (2020) study, it was found that the rate of Pap smear test for women with a family history of cancer was significantly higher. These findings are important in terms of demonstrating that women who feel at risk of cervical cancer are more motivated to participate in screening programs.

The economic status of women was observed to be a factor affecting all HBM-SCCPST subscale scores. Women with good economic status had higher perceptions of benefits, seriousness, susceptibility, and health motivation. Similar studies have also shown that a low income is an obstacle to a Pap smear test (42-44). Elimination of these structural barriers should be given priority by ensuring the continuity of free screening programs and public service announcements.

CONCLUSION

In conclusion, this study showed that women's perceptions of the benefits and barriers of the Pap smear test were related to their health literacy levels. Health promotion programs should particularly target women of screening age and focus on women with low education levels. Defined attitudes and barriers related to cervical cancer should be addressed in future health services. While planning health services for women, activities should be organized to evaluate and increase health literacy levels. In this context, nurses have important responsibilities because they are in one-to-one contact with women at every stage of life. In particular, they can play an important role in helping women understand the importance of the Pap smear test and encourage them to attend screening regularly. During the provision of care, nurses can positively improve health behaviors by contributing to an increase in women's knowledge of healthy lifestyle behaviors. In addition, it is suggested that nurses evaluate women's health literacy levels at every stage of the education and counseling processes and offer support for women through appropriate strategies. Improving the level of health literacy is the most important step in protecting and improving not only women's health but also the health of children, families, and communities. It is considered that this study will contribute to the development of public health by providing a different perspective on women's behaviors that directly affect their health.

ETHICS

Ethics Committee Approval: Approval was obtained from the Non-invasive Clinical Research Ethics Committee of İstanbul Medipol University on November 25, 2021 (decision no: 1151).

Informed Consent: Participation in the study was on a voluntary basis, and verbal and written informed consent was provided by all participants.

Authorship Contributions

Surgical and Medical Practices: A.D., İ.N.Ö., Concept: A.D., İ.N.Ö., Design: A.D., İ.N.Ö., Data Collection or Processing: İ.N.Ö., Analysis or Interpretation: A.D., Literature Search: A.D., İ.N.Ö., Writing: A.D., İ.N.Ö.

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

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

REFERENCES

1. Spring H. Health literacy and COVID-19. Health Info Libr J 2020;37:171-2.
2. Estrada CAM, Gregorio ER, Kanyasan K, Hun J, Tomokawa S, Dumlao MC, et al. School health promotion in South-East Asia by Japan and partners. Pediatr Int 2020;62:1029-38.
3. Park S, Oh S. Factors associated with preventive behaviors for COVID-19 among adolescents in South Korea. J Pediatr Nurs 2022;62:e69-76.
4. Riiser K, Helseth S, Haraldstad K, Torbjørnsen A, Richardsen KR. Adolescents' health literacy, health protective measures, and health-related quality of life during the Covid-19 pandemic. PLoS One 2020;15:e0238161.
5. Nguyen HC, Nguyen MH, Do BN, Tran CQ, Nguyen TTP, Pham KM, et al. People with Suspected COVID-19 Symptoms Were More Likely Depressed and Had Lower Health-Related Quality of Life: The Potential Benefit of Health Literacy. J Clin Med 2020;9:965.
6. Aydın D, Aba YA. Annelerin Sağlık Okuryazarlığı Düzeyleri ile Emzirme Öz-Yeterlilik Algıları Arasındaki İlişki. Dokuz Eylül Üniversitesi Hemşirelik Fakültesi Elektronik Dergisi 2019;12:31-9.
7. Aktan GV, Özdemir F. Health literacy levels of women in climacteric period. Cukurova Medical Journal 2020;45:352-61.
8. Wang G, Wu L. Healthy People 2020: Social Determinants of Cigarette Smoking and Electronic Cigarette Smoking among Youth in the United States 2010-2018. Int J Environ Res Public Health 2020;17:7503.
9. Kilfoyle KA, Vitko M, O'Conor R, Bailey SC. Health Literacy and Women's Reproductive Health: A Systematic Review. J Womens Health (Larchmt) 2016;25:1237-55.
10. Shahid R, Shoker M, Chu LM, Frehlick R, Ward H, Pahwa P. Impact of low health literacy on patients' health outcomes: a multicenter cohort study. BMC Health Serv Res 2022;22:1148.
11. Coughlin SS, Vernon M, Hatzigeorgiou C, George V. Health Literacy, Social Determinants of Health, and Disease Prevention and Control. J Environ Health Sci 2020;6:3061.
12. World Health Organization. Cancer. (2018). Available from: https://www.who.int/news-room/fact-sheets/detail/cervical-cancer Accessed: 05.06.2024
13. Türkiye Kanser İstatistikleri, 2017. Ankara, 2021. Available from: https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/Dokumanlar/Istatistikler/Turkiye_Kanser_Istatistikleri_2017_OZETLI.pdf Accessed: 05.06.2024
14. Vaccarella S, Georges D, Bray F, Ginsburg O, Charvat H, Martikainen P, et al. Socioeconomic inequalities in cancer mortality between and within countries in Europe: a population-based study. Lancet Reg Health Eur 2022;25:100551.
15. Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health 2023;11:e197-206.
16. Uludağ G, Gamsızkan Z, Sungur MA. Evaluation of Women's Health Beliefs about Cervical Cancer and Screening. Journal of Duzce University Health Sciences Institute 2020;10:357-62 .
17. Kızılırmak A. The Factors Influencing Health Beliefs About Cervical Cancer and Pap Smear Test Among The Women At A University. Journal of Continuing Medical Education 2018;27:165-75.
18. Cetisli NE, Top ED, Işık G. Cervical cancer and pap smear test health beliefs and health-promoting lifestyle of women in Turkey. International Journal of Caring Sciences 2016;9:630–9.
19. Büyükkayacı DN, Yüksel KD, Albayrak SA. Kırk Yaş üstü kadınların meme ve serviks kanseri taramalarına yönelik bilgi ve uygulamaları. Journal of Academic Research in Nursing 2015;1:30–8.
20. Okyay P, Abacıgil F, editörler. Türkiye sağlık okuryazarlığı ölçekleri güvenilirlik ve geçerlilik çalışması. (Turkish). Ankara: Ministry of Health; 2016. Available from: https://ekutuphane.saglik.gov.tr/Yayin/530 Accessed: 05.06.2024
21. Guvenc G, Akyuz A, Açikel CH. Health Belief Model Scale for Cervical Cancer and Pap Smear Test: psychometric testing. J Adv Nurs 2011;67:428-37.
22. Dost A, Özsoy Durmaz M. Health Literacy Levels of Individuals with Chronic Diseases and Affecting Factors. Journal of İnönü University Vocational School of Health Services 2022;10:652-66.
23. Humphrys E, Burt J, Rubin G, Emery JD, Walter FM. The influence of health literacy on the timely diagnosis of symptomatic cancer: A systematic review. Eur J Cancer Care (Engl) 2019;28:e12920.
24. Kendir C, Kartal M. Health literacy levels affect breast cancer knowledge and screening attitudes of women in Turkey: A descriptive study. Turkish Journal of Public Health 2019;17:183-94.
25. Ducray JF, Kell CM, Basdav J, Haffejee F. Cervical cancer knowledge and screening uptake by marginalized population of women in inner-city Durban, South Africa: Insights into the need for increased health literacy. Womens Health (Lond) 2021;17:17455065211047141.
26. Eo YS, Kim JS. Associations of health belief and health literacy with Pap smear practice among Asian immigrant women. Eur J Oncol Nurs 2019;42:63-8.
27. Gallo F, Caprioglio A, Castagno R, Ronco G, Segnan N, Giordano L. Inequalities in cervical cancer screening utilisation and results: A comparison between Italian natives and immigrants from disadvantaged countries. Health Policy 2017;121:1072-8.
28. Idehen EE, Korhonen T, Castaneda A, Juntunen T, Kangasniemi M, Pietilla AM, et al. Factors associated with cervical cancer screening participation among immigrants of Russian, Somali and Kurdish origin: a population-based study in Finland. BMC Womens Health 2017;17:19.
29. Mortensen JH, Bigaard J, Kvernrød AB. Young Danish HPV vaccinated women's knowledge, barriers and facilitators towards cervical cancer screening: A qualitative study. Prev Med Rep 2021;24:101507.
30. Aweke YH, Ayanto SY, Ersado TL. Knowledge, attitude and practice for cervical cancer prevention and control among women of childbearing age in Hossana Town, Hadiya zone, Southern Ethiopia: Community-based cross-sectional study. PLoS One 2017;12:e0181415.
31. Acharya Pandey R, Karmacharya E. Cervical cancer screening behavior and associated factors among women of Ugrachandi Nala, Kavre, Nepal. Eur J Med Res 2017;22:32.
32. Deguara M, Calleja N, England K. Cervical cancer and screening: knowledge, awareness and attitudes of women in Malta. J Prev Med Hyg 2021;61:E584-92.
33. National Cancer Information Center. 2017. Cervical cancer. Available from: https://www.cancer.go.kr/ lay1/program/S1T211C223/cancer/view.do?cancer_seq=4877/
34. Sağlık Bakanlığı Serviks Kanseri Tarama Programı Ulusal Standartları, 2012. Ankara. Available from: https://hsgm.saglik.gov.tr/depo/Mevzuat/Genel_Nitelikli_Yazi_ve_Gorusler/Serviks_

Kanseri_Tarama_Programi_Ulusal_Standartlari.pdf Accessed: 05.06.2024

35. Musa J, Achenbach CJ, O'Dwyer LC, Evans CT, McHugh M, Hou L, et al. Effect of cervical cancer education and provider recommendation for screening on screening rates: A systematic review and meta-analysis. PLoS One 2017;12:e0183924.
36. Ayaz-Alkaya S, Ozturk FO. Health Literacy Levels of Women and Related Factors in Turkey. J Nurs Res 2021;29:e180.
37. Huang CH, Talley PC, Lin CW, Huang RY, Liu IT, Chiang IH, et al. Factors associated with low health literacy among community-dwelling women in Taiwan. Women Health 2020;60:487-501.
38. Liu C, Wang D, Liu C, Jiang J, Wang X, Chen H, et al. What is the meaning of health literacy? A systematic review and qualitative synthesis. Fam Med Community Health 2020;8:e000351.
39. Bakan AB, Yıldız M. A Study on Determining the Health Literacy Levels of Individuals Aged 21-64. Health and Society 2019;29:33-40.
40. Chorley AJ, Marlow LAV, Forster AS, Haddrell JB, Waller J. Experiences of cervical screening and barriers to participation in the context of an organized programme: a systematic review and thematic synthesis. Psychooncology 2017;26:161-72.
41. Kim H, Mahmood A, Carlton E, Goldsmith J, Chang C, Bhuyan S. Access to Personal Health Records and Screening for Breast and Cervical Cancer Among Women with a Family History of Cancer. J Cancer Educ 2020;35:1128-34.
42. Abulizi G, Abulimiti T, Li H, Abuduxikuer G, Mijiti P, Zhang S, et al. 2018. Knowledge of cervical cancer and Pap smear among Uyghur women from Xinjiang, China. BMC Women's Health 2018;18:21-8.
43. Harcourt N, Ghebre RG, Whembolua GL, Zhang Y, Warfa Osman S, Okuyemi KS. "Factors associated with breast and cervical cancer screening behavior among African immigrant women in Minnesota." Journal of Immigrant and Minority Health 2014;16:450-6.
44. Forney-Gorman A, Kozhimannil KB. Differences in Cervical Cancer Screening Between African-American Versus African-Born Black Women in the United States. J Immigr Minor Health 2016;18:1371-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:168-177
DOI: 10.4274/BMJ.galenos.2024.2023.8-8

Research

Nurses' Views on Distance in-service Trainings

Hemşirelerin Uzaktan Hizmet İçi Eğitimlere İlişkin Görüşleri

Figen Çalışkan[1], Emine Şenyuva[2], Merih Çavuşlu[3]

[1]Trakya University Faculty of Health Sciences, Department of Nursing Education, Edirne, Türkiye

[2]İstanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, Department of Nursing Education, İstanbul, Türkiye

[3]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Departmant of Management, İstanbul, Türkiye

ABSTRACT

Objective: The in-service training aims to maintain nurses' individual and professional development, update their existing knowledge and skills, ensure their adaptation to new tasks, develop their professional identity, develop their creativity, increase the quality/quality of the care they provide, improve individual and institutional productivity, and prevent work accidents and errors. The research aimed to discover nurses' views about in-service distance training.

Methods: The study used a qualitative research design. The research was conducted with 45 nurses who volunteered to participate. The data were collected using the information form and semi-structured individual interview form. In the analysis of qualitative data, "content analysis technique" was used.

Results: The results of the research were collected under six main themes: In-service distance training's contributions to professional development, in-service distance training's strengths, in-service distance training's weaknesses, in-service distance training's problems, solutions to these problems, and preferred in-service training environment. Nurses indicated that they preferred blended training the most.

Conclusion: Determining nurses' views about distance education may provide clues about the structuring of distance in-service training and the effective use of resources. Therefore, it can also improve the quality of nursing care.

Keywords: Continuing education, distance in-service training, in-service training, nurse

ÖZ

Amaç: Hizmet içi eğitim, hemşirelerin bireysel ve mesleki gelişimlerini sürdürmeyi, mevcut bilgi ve becerilerini güncellemeyi, yeni görevlerine uyumlarını sağlamayı, mesleki kimliklerini geliştirmeyi, yaratıcılıklarını geliştirmeyi, verdikleri bakımın niteliğini/kalitesini artırmayı, iş kazalarını ve hatalarını önlemeyi amaçlamaktadır. Araştırma, hemşirelerin hizmet içi uzaktan eğitime ilişkin görüşlerini ortaya koymayı amaçlamıştır.

Gereç ve Yöntem: Çalışma nitel araştırma desenindedir. Araştırma, araştırmaya katılmaya gönüllü olan 45 hemşire ile yürütülmüştür. Veriler bilgi formu ve yarı yapılandırılmış bireysel görüşme formu kullanılarak toplanmıştır. Nitel verilerin analizinde "içerik analizi tekniği" kullanılmıştır.

Bulgular: Araştırma sonuçları altı ana tema altında toplanmıştır: Hizmet içi uzaktan eğitimin mesleki gelişime katkıları, hizmet içi uzaktan eğitimin güçlü yönleri, hizmet içi uzaktan eğitimin zayıf yönleri, hizmet içi uzaktan eğitimin sorunları, bu sorunlara yönelik çözüm önerileri ve tercih edilen hizmet içi eğitim ortamı. Hemşireler en çok karma eğitimi tercih ettiklerini belirtmişlerdir.

Sonuç: Hemşirelerin uzaktan eğitime ilişkin görüşlerinin belirlenmesi, uzaktan hizmet içi eğitimin yapılandırılması ve kaynakların etkin kullanımı konusunda ipuçları verebilir. Böylece hemşirelik bakımının kalitesi de artırılabilir.

Anahtar Kelimeler: Sürekli eğitim, uzaktan hizmet içi eğitim, hizmet içi eğitimi, hemşire

Address for Correspondence: Emine Şenyuva, İstanbul University-Cerrahpaşa Florence Nightingale Faculty of Nursing, Department of Nursing Education, İstanbul, Türkiye
Phone: +90 212 440 00 03 - 27504 E-mail: esenyuva@iuc.edu.tr ORCID ID: orcid.org/0000-0001-8855-6692

Cite as: Çalışkan F, Şenyuva E, Çavuşlu M. Nurses' Views on Distance in-service Trainings. Med J Bakirkoy 2024;20:168-177

Received: 17.08.2023
Accepted: 29.05.2024

INTRODUCTION

Today, rapid and significant changes and developments in scientific knowledge and technology and health services have occurred. This situation requires nurses to update their knowledge and skills throughout their professional life and acquire up-to-date knowledge and skills. This requires continuous education and training for nurses as lifelong learners (1,2). In-service nursing training is an educational activity designed to ensure that nurses acquire and maintain the competencies they need to perform the tasks and responsibilities that employers expect (3).

In-service nursing training is an educational activity designed to ensure that nurses acquire and maintain the competencies required to perform the tasks and responsibilities that employers expect. The in-service training that is conducted to achieve these goals is mainly face-to-face. These in-service trainings aim to maintain nurses' individual and professional development, update their existing knowledge and skills, ensure their adaptation to new tasks, develop their professional identity, develop their creativity, increase the quality/quality of the care they provide, improve individual and institutional productivity, and prevent work accidents and errors (4). However, there are problems with most face-to-face in-service trainings, such as ignoring the needs of departments where nurses work as well as the training needs, training consisting mainly of theoretical knowledge with little or no application, failure to use different teaching methods and techniques, inadequate scheduling of training, inadequate physical and technical equipment, and lack of experts among educators (4,5). Due to a large number of nurses working in the health sector and the difficulty of providing on-site training, in-service distance training (ISDT) is preferred as it enables nurses to train wherever and whenever they want, overcome time and geographical barriers, and access distance education to ensure equity in training, enable more nurses to train at a lower cost, allow nurses to continue their education while working without interrupting their professional and personal commitments, provide opportunities to benefit from experts/lecturers in different locations, and provide individual learning opportunities (2,5).

Reviewing the literature, a limited number of international and national studies have shown the views and experiences of nurses with ISDT and the effectiveness of these trainings (1,2). In this context, this study is important to get an idea of nurses' inclination toward distance education, find out nurses' views on the strengths and weaknesses of ISDT, structure ISDT according to these views, and give indications on the effective use of resources. This shows that the current research can meet a need and makes the research valuable. This study reports on a study that sought to answer the following research questions:

1. What is the contribution of ISDT to nurses' professional development?

2. What are the strengths of ISDT?

3. What are the weaknesses of ISDT?

4. What problems do nurses encounter with ISDTs? What suggestions do nurses have for solving these problems?

5. Which environment do nurses prefer for in-service training? And why?

METHODS

Aim

This study discovered nurses' views about ISDT.

Design

The study has a qualitative research design.

Participants and Sampling

The study population consisted of all nurses (n=1313) working in a training and research hospital in İstanbul, affiliated with the Ministry of Health. This hospital, where the study was conducted, was selected because part of the in-service training for nurses is conducted face-to-face and another part is conducted via distance training. The maximum variation sampling method was used to determine the sample for the study. Care was taken to select nurses who work in different departments and positions, have diverse professional experiences, and have participated in both face-to-face and ISDT. The study was conducted with 45 nurses who volunteered to participate in the study.

Instruments

The data were collected using the information form and semi-structured individual interview form.

Information Form: Developed by the researchers following the literature (1,4). The form contained eight questions to identify the sociodemographic (age, gender, marital status, education level, etc.) and occupational characteristics of the nurses (length of service as a nurse, task, unit worked, etc.).

Semi-Structured Individual Interview Form: Developed by researchers from the literature (1,6). The semi-structured individual interview form contained five open-ended questions to elicit the nurses' individuals, in-depth, and detailed views about ISDT.

Data Collection

Data were collected through one-on-one interviews following the questions in the information form and semi-structured individual interview form at the hospital between October 15 and December 15, 2020. A suitable room was arranged for the interviews. The opinions of the participants were recorded using the semi-structured individual interview form.

Interviews with the nurses lasted approximately 25-30 minutes. During the interviews, care was taken not to disturb the nurses' views so as not to deviate from the aim of the questions and to obtain rich and in-depth views. During the interview, in addition to the questions in the semi-structured individual interview form, sub-questions were asked as needed, and the discussion was terminated when data saturation was reached (6-8).

The questions in the semi-structured individual interview form were subjected to the evaluation of three experts, two faculty members from the field of nursing and one faculty member from the field of education, in terms of their suitability and comprehensibility for the research purpose and theoretical framework. Improvements were made as a result of the evaluations. In addition, a pilot application was conducted with three nurses, and the questions in the opinion form were rearranged according to the feedback received during the pilot application. The three nurses who participated in the pilot study were excluded from the sample.

Ethical Considerations

Ethics Committee approval was obtained from University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2019-17-17, date: 02.09.2019). Institutional approval (date: 02.10.2019, number: 5) was obtained from the institution where the research would be conducted. Verbal and written informed consent was obtained from the nurses who agreed to participate in the study at the beginning of the interview.

Statistical Analysis

Forty-five nurses were included in the study, and their opinions were analyzed. The researchers analyzed the opinions obtained using the content analysis method, a qualitative data analysis technique. While the analysis was conducted, the opinions obtained with semi-structured interviews were first conceptualized, and then the main themes, which were logically ordered according to the emerging concepts and explained the data accordingly, were determined. To analyze and compare the different meanings of the themes, sub-themes were created according to the nurses' responses to the research questions related to the purpose of the study. Thus, an attempt was made to obtain more detailed and in-depth information from qualitative analyses (8). The themes obtained were grouped under six main themes and 47 sub-themes related to nurses' views on ISDT. The qualitative data obtained from the themes and sub-themes that emerged from the analysis were digitized for research purposes and presented with quotes from the nurses' views. Age (A), gender (F/M), and roles of the nurses whose views were quoted [operating room nurse (ORN), training nurse (TN), intensive care nurse (ICN), outpatient clinic nurse (OCN), service nurse (SN), and charge nurse (CN)] are indicated in brackets at the end of the quotes.

RESULTS

The mean age of the nurses was 30.49±8.42 (minimum: 21, maximum: 57 years), and nine nurses worked in internal departments, nine in intensive care, and nine in the emergency department. The nurses' demographic information is presented in Table 1.

Data obtained from nurses' views on ISDT were collected under six main themes (Table 2).

Theme 1: The contribution of ISDT to professional development.

This theme is defined as an adaptation to the institution/profession (n=29), acquisition of new knowledge and skills (n=28), development/updating of knowledge and skills (n=23), delivery of skilled nursing care (n=22), opportunity to use technology (n=21), raise awareness of technological changes and developments (n=21), sharing knowledge and skills among nurses (n=13), prevention of occupational accidents (n=7), acquisition of communication skills (n=6), no professional contribution (n=4) under ten sub-themes (Table 2).

"Information and technology are fundamental elements of health care. Moreover, they are changing rapidly and continuously. As members of the profession, we must adapt to these changes, keep up with innovations, and keep up with developments. Only then can we improve the quality of care we provide." (37, F, SN)

"... From time to time, I feel that I am inadequate. The behaviors of the students I professionally supervise, their communication skills, and their approach to events can change depending on the time and conditions. I also need to attend in-service trainings to keep up with this situation and communicate better with new generations." (26, F, SN)

"I have not been able to improve in any of the in-service trainings I have attended so far. I think most trainings do not aim to improve/update the knowledge we have; they contain information based on memorization and are made to be done." (24, F, SN)

Theme 2: ISDT's strengths

This theme is defined as allowing for participation in training outside of working hours (n=39), offering flexibility in time and space (n=33), allowing for individualized learning (n=27), giving responsibility for learning (n=26), allows for independent learning (n=26), provides an opportunity for repetition (n=25), provides an enriched educational environment with diverse learning materials (n=21), provides standards in academic programs (n=18), facilitates mass education (n=17), enables more people to benefit from experts (n=15), facilitates easy access to training materials (n=6) under 11 sub-themes (Table 3).

Table 1. Sociodemographic and occupational characteristics of nurses (n=45)

Sociodemographic characteristics		**n**	**%**
Age	Minimum: 21 maximum: 57	30.49±8.42	
Gender	Female	39	86.7
	Male	6	13.3
Marital status	Single	26	57.8
	Married	19	42.2
Educational background	Vocational high school of health services	2	4.4
	Associate degree	4	8.9
	Bachelor's degree	32	71.1
	Graduate (master, doctorate)	7	15.6
Nursing experience	0-5 years	21	46.6
	6-10 years	7	15.6
	11-15 years	7	15.6
	16-20 years	4	8.9
	21 years and above	6	13.3
Tenure in the workplace	0-5 years	14	31.1
	6-10 years	12	26.7
	11-15 years	9	20.0
	16-20 years	5	11.1
	21 years and above	5	11.1
Position	Service nurse	16	35.6
	Charge nurse	13	28.9
	Executive nurse	5	11.1
	Training nurse	2	4.4
	Other	9	20.0
Department	Internal deparments	9	20.0
	Intensive care	9	20.0
	Emergency	9	20.0
	Surgical unit	7	15.5
	Operating room	5	13.3
	Administration	2	4.4
	Training	2	4.4
	Outpatient clinic	2	4.4

"In distance education, the subject taught by a single expert is offered to nurses working in facilities in different locations. Thus, training becomes standard. Also, the fact that the training is not tied to a specific period makes it easier for us to receive the training in the setting and at the time we want." (43, F, CN)

"...It is an advantage that we have the opportunity to replay the incomprehensible topics, hear them often." (41, F, ICN)

"...the lack of a time limit in class, the fact that the topics are not just lectures and that they are presented with different teaching materials attract our attention, and I think that eliminates the monotony of teaching…" (46, F, CN)

"...It ensures that many more people in different places and at different times can benefit from the same training content... Also, we do not have to come to the facility for training on our days off..." (33, F, SN)

"Face-to-face training is usually conducted with lectures and slide presentations. Distance training, on the other hand, creates a learning environment enriched with up-to-date information, striking images, and, when necessary, audio commentary and video." (25, F, SN)

Theme 3: ISDT's weaknesses

This theme is defined as limited/absent interaction between teachers and learners (n=38), the need to attend training on days off (n=28), lack of skill-based behaviors (n=27), the theoretical focus of training (n=24), no feedback to nurses at the end of the training (n=18), and the requirement for skills in using technology (n=11) under six sub-themes (Table 3).

"During distance learning, I cannot ask the questions I want to ask, and I cannot find immediate answers to my questions. This is because communication and interaction are either nonexistent or very weak. Therefore, I find it boring and insincere." (27, F, SN)

"The content was good, but it becomes monotonous; you think you have to finish the training as soon as possible." (35, M, SN)

"...the applications require some computer skills and some infrastructure, so I could not follow it at home, but only in my free time at work..." (46, F, ORN)

"... I had to sacrifice my private work, my free time, and me days off to attend the trainings." (34, M, SN)

"... The content of the training is mainly based on theoretical knowledge. Theoretical information is also taught in too much detail. Unfortunately, training aimed at skill acquisition and practice is never provided..." (45, F, SN)

Theme 4: ISDT's problems

This theme is defined as not being in line with nurses' interests/wants and needs (n=27). Training is not aligned with their work (n=26), lack of/limited interaction between instructor and nurse during training (n=25), the theoretical focus of training (n=21), no support for training through different teaching methods and materials (n=19), instructors are not well equipped and are not experts in their field (n=18), long training duration (n=14), No feedback to nurses at the end of training (n=12), insufficient number of training (n=10) under nine sub-themes (Table 4).

"Many of the in-service trainings organized were not focused on my interests and needs; I could not focus because they were conducted top-down." (29, F, D-SN)

"I work in the children's department." There are almost no ISDTs related to my specialty. However, I need more training in the area in which I work. However, there are more general trainings offered on various topics that I do not feel are necessary..." (27, F, D-SN)

"A lot of the in-service trainings I have attended have had theoretical content. I just listened; we did not do anything. The training should be enriched with different methods so that you can practice and acquire skills." (41, F, ICN)

"Since the organized in service education was not supported with documents, I forgot what I listened to after a while. When it is supported with different documents, the permanence of the training will increase." (26, F, SN)

Table 2. Nurses' views on the contribution of in-service distance training to professional development (n=45)

Main theme	Sub-theme	n	%
The contribution of in-service distance training to professional development	Adaptation to the institution/profession	29	64.4
	Acquisition of new knowledge and skills	28	62.2
	Development/updating of knowledge and skills	23	51.1
	Delivery of skilled nursing care	22	48.9
	Opportunity to use technology	21	46.7
	Raise awareness of technological changes and developments	21	46.7
	Sharing knowledge and skills among nurses	13	28.9
	Prevention of occupational accidents	7	15.6
	Acquisition of communication skills (other team members, patients, and relatives, etc.)	6	13.3
	No professional contribution	4	8.9

Table 3. Nurses' views on the strengths and weaknesses of in-service distance training (n=45)

Main theme	Sub-theme	n	%
In-service distance training's strengths	Possibility to participate in trainings outside working hours	39	86.7
	Flexibility in time and space	33	73.3
	Providing individual learning	27	60.0
	Gaining responsibility for learning	26	57.8
	Independent learning	26	57.8
	Opportunity for repetition	25	55.6
	An enriched educational environment with diverse learning materials	21	46.7
	Provision of standards in academic programs	18	40.0
	Facilitating mass education	17	37.8
	Enabling more people to benefit from experts	15	33.3
	Easy access to training materials	6	13.3
In-service distance training's weaknesses	Limited/absent interaction between teachers and learners	38	84.4
	Having to participate in training on days off	28	62.2
	Lack of acquisition of skill-oriented behaviors	27	60.0
	The theoretical focus of the training	24	53.3
	No feedback to nurses at the end of the training	18	40.0
	Requires technological knowledge	11	24.4

"…When instructors become experts in their field, the training is more effective. The instructor should be able to expand my horizons on the topic, point me to various resources on the topic, and teach me how to access those resources…" (32, F, OCN)

The theme 5: Suggested solutions to the problems encountered at the ISDT

This theme is defined as taking nurses' demands and needs into consideration (n=32), focusing the training on their work area (n=29), strengthening the interaction between instructor and nurse in training (n=23), supporting training through different teaching methods and materials (n=17), selecting educators from well-equipped and knowledgeable individuals (n=15), planning training based on skill acquisition (n=14), providing feedback to nurses at the end of training (n=11), and increasing the number of trainings (n=12) under eight subthemes (Table 4).

"...Training should be planned according to the training needs of the nurses... Trainings should be scheduled accordingly. So our desire to attend the trainings will be stronger..." (33, F, CN)

"…The trainings should be organized according to the nurses' work areas in different departments and their specialties." (27, F, TN)

"…in the group face-to-face trainings, a question that does not come to your mind at that moment or that you could not ask can come to someone else's mind and be asked. For this reason, in-service distance learning should be organized to enhance the interaction between the instructor and the nurse…" (44, F, ICN)

"... Experts should select educators in their field. This will ensure that we participate willingly in the training and make the training more effective and efficient..." (37, F, CN)

"...The number of ISDTs should be increased, and nurses should be encouraged to attend these trainings..." (29, F, ORN)

Theme 6: The preferred ISDT environment

This theme is defined as face-to-face teaching (n=21), distance teaching (n=11), and blended learning (face-to-face and distance teaching together) (n=13) under three subthemes (Table 5).

Table 4. Nurses' views on the problems they experienced in in-service distance training (n=45)

Main theme	Sub-theme	n	%
In-service distance training's problems	Not in line with nurses' demands and needs	27	60.0
	Training is not in line with their work	26	57.8
	Lack of/limited interaction between instructor and nurse during training	25	55.6
	The theoretical focus of the training	21	46.7
	No support of training through different teaching methods and materials	19	42.2
	Instructors are not well equipped and are not experts in their field	18	40.0
	Long training periods	14	31.1
	No feedback to nurses at the end of the training	12	26.7
	Insufficient number of trainings	10	22.2
Suggested solutions to the problems encountered at in-service distance training	Consideration of nurses' interests/wants and needs	32	71.1
	The trainings focused on their work	29	64.4
	Strengthening the interaction between educators and nurses in the trainings	23	51.1
	Supporting training through different teaching methods and materials	17	37.8
	Selecting educators who are well equipped and experts in the field	15	33.3
	Planning training sessions that are focused on skill acquisition	14	31.1
	Providing feedback to nurses at the end of the training	12	26.7
	Increasing the number of trainings	11	24.4

Table 5. Nurses' views on their preferred in-service environment (n=45)

Main theme	Sub-theme	n	%
Preferred in-service training environment	Face-to-face education	21	46.7
	Distance education	11	24.4
	Blended learning (face-to-face and distance education together)	13	28.9

"... I prefer face-to-face training. Because when I meet with other colleagues, communicate with them, exchange ideas, and talk about the training, the training is more effective for me..." (37, F, OCN)

"I prefer distance training (ISDT) because it is more convenient in terms of time and location. I can attend training in an environment where I feel more comfortable and whenever I want. I am not dependent on the training environment, training time, or duration. I can attend training whenever and wherever I want. I can learn me by repeating as much as I want by accessing the materials..." (33, M, CN)

"Distance learning... It allows me to update my professional knowledge while working. It also allows me to attend training outside work hours." (40, F, CN)

"It can vary depending on the topic and type of training. Distance learning can be done if the training content is only theoretical information and is mainly about updating and remembering information. The application and interactive parts, the skills, can be taught in face-to-face classes…" (27, F, TN)

DISCUSSION

The findings on the six major themes that emerged from the nurses' opinions were discussed under the headings of contributions of ISDT to professional development, strengths and weaknesses of ISDT, problems in ISDT, solutions to these problems, and preferred ISDT environment.

In the study, nurses' views on the professional contributions of ISDT were related to institutional/professional adaptation, acquisition of new knowledge and skills, and development/updating of knowledge and skills, etc. (Table 2). The literature states that ISDTs make professional contributions to nursing, such as enabling nurses to continue their individual and professional development, update their existing knowledge and skills, adapt to their new roles, develop their professional identity, increase the quality of care, strengthen communication between team members, increase individual and institutional productivity, prevent occupational accidents and errors, and increase the chance of using technology (4,9). This finding, consistent with the research findings in the literature, was taken as an indication that nurses are optimistic about ISDT and are aware of the personal and professional contributions of in-service training.

The study found that nurses perceived the strengths of ISDT to be the opportunity to participate in ISDT outside working hours, flexibility of time and place, individual learning, and a learning environment enriched with various teaching materials, etc. (Table 3). In the research of Tavares et al. (10) and Sari and Nayır (11) the strengths of ISDT are seen in the fact that they allow employees to attend in-service training whenever and wherever they want, without reducing their work pace, performance, and productivity, that they can listen to and re-watch training when they feel it is necessary, and that they enable adults to plan and take responsibility for their learning. In the studies of Tekin (6) and Tavares et al. (10), the richness and quality of learning and teaching resources and materials are important factors that influence the quality of ISDT. This finding, consistent with the results of this study in the literature, indicates that nurses are aware of the strengths of distance education. This finding also shows that nurses cannot effectively and efficiently benefit from in-service training because of their heavy workload during working hours. For this reason, we believe that they would prefer ISDTs more because they offer the opportunity to participate in trainings outside working hours, are flexible in terms of time and location, and offer individual responsibility for learning.

The study identified nurses' views on the weaknesses of ISDT as limited/absent interaction between teachers and learners, having to participate in training on days off, lack of acquisition of competency-based behaviors, and theoretical nature of training (Table 3). In the studies conducted by Tekin (6) and Cheng and Chau (12), one of the weaknesses of distance education is the limited communication and interaction between the instructor and the learner. In the studies conducted by Buğdaylı and Akyürek (9), Öztürk et al. (13), it is found that nurses who have to attend in-service trainings outside their working hours have problems with being reluctant or not attending the trainings, not being able to ask questions, not being able to interact, and not collaborating during the training. This finding, consistent with the results of this study in the literature, indicates that nurses are aware of the weaknesses of distance education.

In the research, the opinions of the nurses about the problems they experienced in ISDT are that it is not conducted following the interests/wants and needs of the nurses, the training is not focused on the areas in which they work, the interaction between the instructor and the nurse in training does not exist / limited, etc. (Table 4). The literature states that ISDTs are ineffective because they are prepared from the top down, far from the individual reality, without considering the needs of the professionals and the differences in the unit/service in which they work, and because the organized trainings are theoretical (14). In face-to-face training, teachers and learners can make eye contact, easily observe each other's behavior and body language in the learning environment, and communicate

one-on-one (12,15). However, since the instructor and the learner are not in the same place in distance learning, they can communicate online. This situation results in the teacher and learner not being able to interact and communicate appropriately because they cannot make eye contact, etc. (16-18). This result led us to believe that nurses cannot sufficiently benefit from these trainings because they do not want to attend the trainings, are reluctant to attend the trainings when they have to attend the trainings, when ISDTs are not conducted mainly by nurses' interests/requirements and needs, when there is little or no interaction between the instructor and nurse in the trainings, when the trainings are theoretical, and when the appropriate timing is not determined. Furthermore, this finding was interpreted to mean that ISDTs should be structured to address their weaknesses and problems.

In the study, nurses' views on solutions to the problems they experienced in ISDT were determined by considering nurses' wants and needs, focusing training on their working areas, increasing instructor-nurse interaction in training, and supporting training with different teaching methods and materials, etc. (Table 4). Tekin (6) and Chaghari et al. (4) recommend that to improve ISDTs, ISDTs should be conducted in small groups, the demands and needs of participants should be considered, evaluation criteria should be set, feedback should be provided, the number and quality of training should be increased, different methods should be used, instructors should be selected from qualified and experts in their field, and training should be planned based on experience. In the studies of Chaghari et al. (4), Taşlıbeyaz et al. (5), the need for in-service training should be well analyzed, realistic goals should be set, materials should be prepared according to the condition, and strategies should be developed for all these situations. This finding, consistent with the research findings in the literature, was interpreted to mean that there is a need to identify nurses' educational interests/desires and needs, organize training according to these desires and conditions, and incorporate adult learning principles in training.

Most nurses indicated that they preferred in-service training, face-to-face education, and blended education (face-to-face and distance education together) (Table 5). Similar to the research findings, in the studies by Sindiani et al. (18), Ramos-Morcillo et al. (19), and Barisone et al. (20), it is found that nurses prefer these environments because they believe that face-to-face education is more effective for skill acquisition and distance education should be used for sharing theoretical parts. Nurses who prefer distance learning prefer it because it allows participation in training outside working hours, offers flexibility in time and place, allows individual learning, and provides the possibility of repetition. In the research conducted by Boz Yüksekdağ (21), it was found that nurses could not attend in-person training during working hours, leaving the workplace while working is a problem, the number of nurses who can be assigned to the task is insufficient, and the department manager does not give permission to the nurse. This result, consistent with the research findings in the literature, suggested that in-service training should be structured to include both face-to-face and distance learning to be more effective and efficient and achieve the desired goals.

The study focused on some nurses in one training and research hospital. Therefore, the findings should not be generalized to the entire population.

CONCLUSION

According to the research findings, ISDT helps nurses to adapt professionally to the institution/profession, acquire new knowledge and skills, develop/update knowledge and skills, and provide skilled nursing care. Nurses indicated that the strengths of ISDT are that it provides opportunities for professional development/training while working, independence of time and place, and individual learning. Nurses cited limited/absent interaction between teachers and learners, the need to attend training on days off, and the inability to acquire skill-based behaviors, etc., as weaknesses of ISDT. Nurses indicated that the problems they experienced in ISDT were that training was not delivered according to their interests/requirements and needs, training was not focused on the areas in which they worked, the interaction between instructor and nurse in training was absent/limited, training was theoretical, etc. In addition, nurses indicated that they preferred in-service training, face-to-face training, and blended training (face-to-face and distance) the most.

In line with these research findings, the following suggestions are made. The in-service training environment should be determined by the content and purpose of the topic to be taught. The distance education method can be used in in-service training for theoretical knowledge, repetition, and information. However, training that requires practice and interaction should be conducted face-to-face or blended. Before planning ISDTs, needs assessment studies should be conducted, and the need for in-service training for nurses should be identified on the basis of the findings. It should be planned, implemented, and evaluated according to the identified training needs. It should include attention-grabbing and timely topics related to developments and changes in the nurse's work areas. It should be enriched

with various teaching methods and materials that reinforce the interaction between the instructor and nurses and teach skill-based behaviors. Studies should be conducted with different sample groups to examine the persistence of the knowledge, skills, and attitudes to be acquired in ISDTs and the effectiveness of the training.

Rapid and significant changes and developments in scientific knowledge technology and health services have occurred continually. All these changes and developments require nurses' knowledge and skills throughout their professional life to acquire up-to-date knowledge and skills. Managers have a great responsibility in planning, organizing in-service trainings, and providing training to nurses at regular intervals. Determining the nurses' views about distance education may provide clues about the structuring of distance in-service training and the effective use of resources. Therefore, it can also improve the quality of nursing care.

Acknowledgments

We are grateful for the contributions of the participants.

ETHICS

Ethics Committee Approval: Ethics Committee approval was obtained from University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2019-17-17, date: 02.09.2019). Institutional approval (date: 02/10/2019, number: 5) was obtained from the institution where the research would be conducted.

Informed Consent: Verbal and written informed consent was obtained from the nurses who agreed to participate in the study at the beginning of the interview.

Authorship Contributions

Surgical and Medical Practices: F.Ç., M.Ç., Concept: F.Ç., E.Ş., Design: F.Ç., E.Ş., M.Ç., Data Collection or Processing: F.Ç., M.Ç., Analysis or Interpretation: F.Ç., E.Ş., M.Ç., Literature Search: F.Ç., E.Ş., M.Ç., Writing: F.Ç., E.Ş., M.Ç.,

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

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

REFERENCES

1. Safaeifard N, Areshtanab HN, Roshangar F, Ebrahim H, Moonaghi HK, Janani R. Preferred learning styles of nurses in in-service training courses in Tabriz University of Medical Sciences. Acta Facultatis Medicae Naissensis 2019; 36: 69-78. DOI: 10.2478/afmnai-2019-0007.
2. Maria L, Kiriaki T, Christos I, Aikaterini F, Lambrini K. Continuing distance education in nursing. EAS Journal of nursing and Midwifery 2019; 1: 155-160. DOI:10.36349/EASJNM.2019.v01i05.002.
3. Şenvuva E. Nurses continuing education with the approach of distance education. International Journal of Social Sciences & Interdisciplinary Research 2012; 1: 47-56. (Original work published in Turkish).
4. Chaghari M, Saffari M, Ebadi A, Ameryoun A. Empowering education: A new model for in-service training of nursing staff. Journal of Advances in Medical Education & Professionalism 2017; 5: 26-32. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5238493/pdf/JAMP-5-26.pdf. (accessed 10 April 2021).
5. Taşlıbeyaz E, Karaman S, Göktaş Y. Examining the experiences of teachers received in service training through distance education. Ege Education Journal 2014; 15: 139-160. (Original work published in Turkish).
6. Tekin O. Investigation of teachers' views on distance learning in-service training programs. Eğitimde Kuram ve Uygulama 2020; 16: 20-35. (Original work published in Turkish).
7. Baltacı A. The qualitative research process: How to conduct a qualitative research. Ahi Evran Üniversitesi Sosyal Bilimler Enstitüsü Dergisi 2019; 5: 368-388. https://doi.org/10.31592/aeusbed.598299. (Original work published in Turkish).
8. Yıldırım A, Şimşek H. Sosyal bilimlerde nitel araştırma yöntemleri. 11. Ed. Ankara: Seçkin Yayıncılık; 2018.
9. Buğdaylı G, Akyürek ÇE. The views of nurses about on-the-job training activites: A sample of a university hospital. Hemşirelikte Araştırma Geliştirme Dergisi 2017; 19: 14-25. Available from: https://dergipark.org.tr/en/download/article-file/986914. (accessed 8 April 2021). (Original work published in Turkish).
10. Tavares APC, Leite BS, Silveira IA, dos Santos TD, de Brito WAP, Camacho ACLF. Analysis of Brazilian publications on distance education in nursing: integrative. Rev Bras Enferm 2018; 71: 214-222. https://doi.org/10.1590/0034-7167-2016-0454.
11. Sari T, Nayır F. Challenges in distance education during the (covid-19) pandemic period. Qualitative Research in Education 2020; 9: 328-360. doi:10.17583/qre.2020.5872.
12. Cheng G, Chau J. Exploring the relationships between learning styles, online participation, learning achievement and course satisfaction: An empirical study of a blended learning course. British Journal of Educational Technology 2016; 47: 257-278. https://doi.org/10.1111/bjet.1224.
13. Öztürk H, Kurt Y, Özkan ÇG, Tor E, Kavgacı A. Nursing education opportunities and their educational expectations: The use of computer and technology in education. Sağlıkta Performans ve Kalite Dergisi 2018; 15: 69-83. Available from: https://shgmkalitedb.saglik.gov.tr/Eklenti/30845/0/saglikta-performans-ve-kalite-dergisi-15-sayipdf.pdf#page=69. (accessed 15 April 2021). (Original work published in Turkish).
14. Özkan İ, Taylan S, İlaslan E. The experiences of nursing students towards distance education during the COVID-19 pandemic. International e-Journal of Educational Studies (IEJES) 2021; 5: 106-117. DOI: 10.31458/iejes.942443.
15. Bernstein AG, Isaac C. Critical thinking criteria for evaluating online discussion", International Journal for the Scholarship of Teaching and Learning 2018; 12: Article 11. https://doi.org/10.20429/ijsotl.2018.120211.
16. Abuhammad S. Barriers to distance learning during the Covid-19 outbreak: A qualitative review from parents' perspective. Heliyon 2020; 6: Article e05482.
17. Langegård U, Kiani K, Nielsen SJ, Svensson PA. Nursing students' experiences of a pedagogical transition from campus learning to distance learning using digital tools. BMC Nursing 2021; 20: 1-10. https://doi.org/10.1186/s12912-021-00542-1.

18. Sindiani AM, Obeidat N, Alshdaifat E, Elsalem L, Alwani MM, Rawashdeh H, et al. Distance education during the covid-19 outbreak: a cross-sectional study among medical students in North of Jordan. Annals of Medicine and Surgery 2020; 59: 186-194. DOI: 10.1016/j.amsu.2020.09.036.
19. Ramos-Morcillo AJ, Leal-Costa C, Moral-García JE, Ruzafa-Martínez M. Experiences of nursing students during the abrupt change from face-to-face to e-learning education during the first month of confinement due to COVID-19 in Spain. International Journal of Environmental Research and Public Health 2020; 17: 2-15. DOI: 10.3390/ijerph17155519.
20. Barisone M, Bagnasco A, Aleo G, Catania G, Bona M, Scaglia SG, Zanini M, Timmins F, Sasso L. The effectiveness of web-based learning in supporting the development of nursing students' practical skills during clinical placements: A qualitative study. Nurse Education in Practice 2019; 37: 56-61. https://doi.org/10.1016/j.nepr.2019.02.009.
21. Boz Yüksekdağ B. Hemşirelik eğitiminde bilgisayar teknolojisinin kullanımı. Açıköğretim Uygulamaları ve Araştırmaları Dergisi 2015; 1: 103-118. Available from: https://dergipark.org.tr/tr/download/article-file/35571 (accessed 8 April 2021). (Original work published in Turkish).

Medical Journal of Bakırköy

Med J Bakirkoy 2024;20:178-181
DOI: 10.4274/BMJ.galenos.2023.2022.3-10

Case Report

Intestinal Ewing Sarcoma Misdiagnosed as an Adnexal Mass in a Young Woman

Genç Kadında Adneksiyal Kitle ile Karışabilen İntestinal Ewing Sarkomu

Pınar Solmaz Hasdemir[1], Aygül Aliyeva[1], Seda Mavili[2], Gamze Göksel[3]

[1]Manisa Celal Bayar University Faculty of Medicine, Department of Obstetrics and Gynecology, Manisa, Türkiye
[2]Manisa Celal Bayar University Faculty of Medicine, Department of Pathology, Manisa, Türkiye
[3]Manisa Celal Bayar University Faculty of Medicine, Department of Medical Oncology, Manisa, Türkiye

ABSTRACT

Extraosseous Ewing's sarcoma is an extremely rare tumor. In the literature, intestinal Ewing's sarcoma was reported in 20 cases, and omental Ewing's sarcoma was reported in only two cases. In this case report, we report a 23-year-old female who presented with the complaint of diffuse abdominal pain. Abdominal ultrasound and whole-body computed tomography revealed a mass starting from the adnexal area and extending between the intestinal loops. Serum levels of tumor markers were high. The serum levels of carbohydrate antigen-125 (CA-125) and carcinoembryonic antigen-19.9 (CA-19.9) were high (427.5 U/mL and 67.9 U/mL, respectively). Laparotomic exploration was performed with the preliminary diagnosis of an adnexal mass, and a mass originating from the small intestine meso and completely covered by the omentum was excised. Histological evaluation reported intestinal and omental origin of Ewing's sarcoma. This case highlights the importance of rare extraosseous Ewing's sarcoma, which should be included in the differential diagnosis of a young female with intra-abdominal mass.

Keywords: Ewing sarcoma, immunohistochemistry, omentum, fluorescence *in situ* hybridization, primitive neuroectodermal tumor

ÖZ

İskelet dışı Ewing sarkomu, oldukça nadir görülür ve intestinal Ewing sarkomu literatürde sırasıyla 20 kez ve omental Ewing sarkomu 2 kez bildirilmiştir. Bu olgu sunumu, yaygın karın ağrısı şikayeti ile başvuran ve ovaryan kitle ön tanısı ile opere edilen 23 yaşında kadın hastaya aittir. Hastaya yapılan abdominal ultrasonografi ve intravenöz kontrastlı batın tomografide adneksiyal alandan başlayarak bağırsak ansları arasına doğru uzanım gösteren kitle saptandı. Tümör markerları yükselmişti [karbonhidrat antijen-125 (CA-125): 427,5; karsinoembriyojenik antijen (CA-19.9): 67,9]. Laparotomide ince bağırsak mezosundan köken alan ve tümü ile omentum ile kaplanmış kitle total olarak eksize edildi ve histolojik olarak Ewing sarkomu tanısı kondu. Bu olgu intraabdominal kitle ile başvuran genç kadın hastada nadir görülen iskelet dışı Ewing sarkomunun ayırıcı tanılarda yer alması gerektiğinin önemini vurgulamaktadır.

Anahtar Kelimeler: Ewing sarkomu, immünohistokimya, omentum, floresan *in situ* hibridizasyon, primitif nöroektodermal tümör

INTRODUCTION

Ewing's sarcoma (EWS) is a small round blue cell tumor characterized by the pathognomonic EWSR 1 gene fusion to a member of the ETS family of transcription factors, creating a novel fusion oncogene crucial to its pathogenesis. EWS is the second most common primary malignant neoplasm of bone after osteosarcoma in the second decade of life. Extraosseous EWS is very rare, and out of 38 reported cases (22 cases in men and 15 cases in women); 3 originated in the esophagus, 9 in the stomach, 5 in the colorectal region, and 20 in the small intestine. EWS, which included the primary omentum, was reported in only 2 cases. The reported cases were in a wide age range from 9 to 68 years.

Here, we present a case of primary intestinal (including omental tissue) EWS that was operated with a prediagnosis of an adnexal mass.

Address for Correspondence: Aygül Aliyeva, Manisa Celal Bayar University Faculty of Medicine, Department of Obstetrics and Gynecology, Manisa, Türkiye
Phone: +90 232 553 901 25 20 E-mail: aygul.aliyeva1992@gmail.com ORCID ID: orcid.org/0000-0003-1997-1408

Cite as: Solmaz Hasdemir P, Aliyeva A, Mavili S, Göksel G. Intestinal Ewing Sarcoma Misdiagnosed as an Adnexal Mass in a Young Woman. Med J Bakirkoy 2024;20:178-181

Received: 12.04.2022
Accepted: 23.04.2023

CASE REPORT

A 23-year-old gravida 0-parity 0 female patient was consulted by the department of general surgery with a complaint of widespread abdominal pain that had been intermittent for about a month and had been getting worse over the last week. The patient's personal and family histories were unremarkable for malignancy and systemic diseases. A 7-8 cm semimobile mass located in the midline of the abdomen was palpated during physical examination. A 90x60x65 mm mass was observed in the midline of the abdomen, at the level of the epigastrium, whose relationship with the intestinal loops could not be distinguished. Both ovaries had a normal appearance, but the potential relationship with the mass could not be excluded because of the close relationship with the mass. The patient was prediagnosed with an ovarian tumor or retroperitoneal Castleman disease. Laboratory tests were unremarkable except for the high tumor marker values: the concentration of carbohydrate antigen-125 (CA-125) was 427.5 U/mL and that of carcinoembryonic antigen-19.9 (CA-19.9) was 67.9 U/mL. In contrasted abdominal computed tomography (CT), the internal genital organs were normal and a 7.5x7.7 cm lobulated solid mass with contrast enhancement, which was connected with the right adnexal lodge and extended upwards between the intestinal loops in the mesentery fatty tissue at the level of the iliac arteries, was observed. The mass continued up to the front of the aorta and vena cava and was pushing the intestines. The origin of the mass could not be clearly determined, and there was an extension toward the right adnexal site and intraperitoneal fluid component, which was more prominent on the right and continued into the pelvis through the cecum, appendix, and peritoneum. No significant retroperitoneal pathological lymph nodes were observed. The other abdominal and retroperitoneal organs were normal (Figure 1).

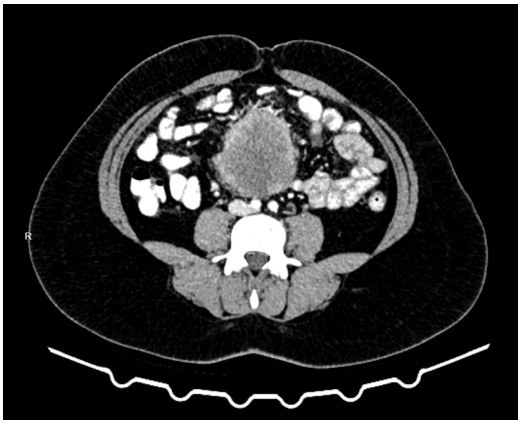

Figure 1. Preoperative appearance of the tumor on pelvic CT
CT: Computed tomography

Laporatomy by superior-inferior median incision was performed. An approximately 8x8 cm necrotic heterogeneous tumoral mass involving the mesos of the small intestine loop starting from approximately 110 cm from Trietz and continuing up to 80 cm distally and omentum was fixed on the tumor. The genital organs had a normal appearance. The omentum covering the mass was partially excised. The frozen section results were reported as lymphoma or neuroendocrine tumor. The intestinal loop with the mass was cut using a TCR55 linear stapler and closed by the general surgery team. The mass with the related small intestinal loop and meso was removed as a block, and end-to-end double-layer isoperistaltic anastomosis was performed. The early postoperative course was uneventful. The patient was discharged on the 6th day following the operation.

Histopathological evaluation revealed extraosseous EWS. The tumor measured 12x10x3 cm and consisted of a nodular mass. On the cut surface, the tumor was composed of solid areas. The solid areas were cream and white, with brown areas representing necrosis and hemorrhage (Figure 2a). Microscopic examination of the tumor revealed cellular areas showing diffuse growth. The

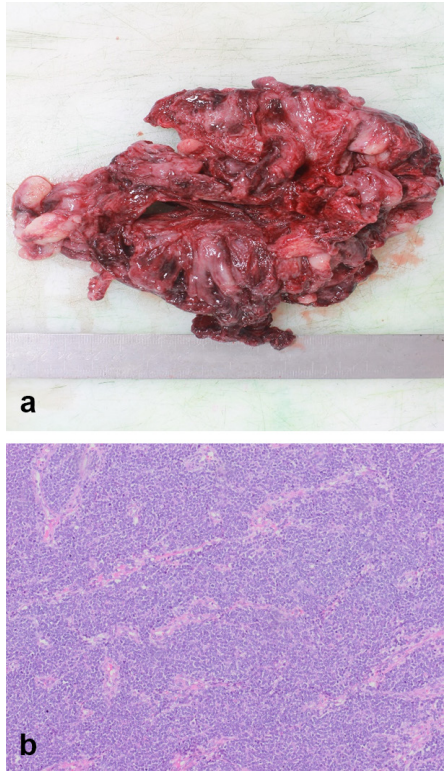

Figure 2. **(a)** Macroscopic appearance of the cut surface of the tumor (8x9 cm in size) composing of white solid, brown necrotic, and hemorrhagic tissue. **(b)** Microscopic appearance of the tumor which is composed of uniform, small, round cells with round nuclei containing fine chromatin, scanty cytoplasm (H& Ex100)

neoplastic cells were uniform, small, and round in shape and had scanty cytoplasm (Figure 2b). Vast areas of necrosis were also observed. Immunohistochemically, tumor cells showed strong and diffuse immunoreaction with CD99 and vimentin, weak immunoreaction with synaptophysin, and focal immunoreaction with CD56.Other neuroendocrine markers such as chromogranin and INSM1 were absent. Other neuroendocrine markers, such as chromogranin and INSM1, were absent. CD45 (LCA) (leukocyte common antigen), CD3, CD20 and TdT (Terminal deoxynucleotidyl transferase) immunohistochemical stains applied to differentiate from lymphoid neoplasms were negative. No immunostaining was detected with desmin, and myogenin was applied to differentiate it from rhabdomyosarcoma. Immunostaining with WT-1 was absent for distinction from desmoplastic small round cell tumor. No immunoexpression was observed with cytokeratin AE1-AE3 and S100. Ki-67 immunohistochemistry revealed a proliferative index of 95 percent. EWRS1 FISH test was performed for tumor-specific diagnosis of undifferentiated small cell sarcoma morphology, and *EWRS1* gene rearrangement was detected. The case was evaluated as an extraskeletal Ewing sarcoma. While the wall of the small bowel resection material was intact, a similar tumor was observed in the meso- and omentectomy material. Widespread lymphovascular invasion was noted in the sections. Metastasis was detected in 8 of 22 lymph nodes extracted from the material (Figure 2).

At the first postoperative month, the patient presented with complaints of fatigue, diffuse free fluid in the abdomen, and diffuse abdominal pain. Laboratory tests were in the normal range except for elevated C-reactive protein (10.15 mg/dL) and decreased albumin (3.2 g/dL) levels. Paracentesis was performed, and 3000 cc of acid fluid was evacuated. Multiple diffuse lesions in the liver and 70x60 mm in size in the right adnexal lodge and 40x40 mm in size in the left adnexal lodge were detected on CT evaluation. Multiple implants were observed in the peritoneum and omentum (Figure 3a). Thorax CT was normal. Magnetic resonance imaging showed results similar to CT. Multiple metastatic masses were observed in the liver parenchyma, most of which were capsular and some were 4-5 cm in size. Peritoneal masses with diffuse intraperitoneal fluid and peritoneal involvement findings not exceeding 1 cm were observed in the upper abdomen. Identified masses were evaluated as liver metastases. In addition, several metastatic implants were observed in the Morrison pouch on the right. An 8x10 cm mass with possible metastatic solid and occasionally cystic areas was observed in the posterior part of the uterus, adhering to the peritoneum toward both adnexal sites and continuing into the Douglas space. Multiple peritoneal, mesenteric, and metastatic masses were noted (Figure 3b).

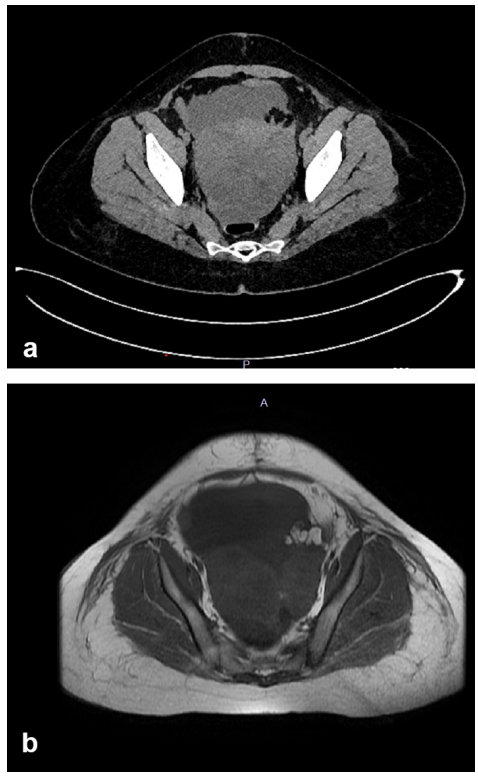

Figure 3. Postoperative 1st-month imaging of the patient at CT **(a)** and MRI **(b)**
CT: Computed tomography, MRI: Magnetic resonance imaging

Ifosfamide, etoposide, vincristine, actinomycin-D, and cyclophosphamide regimen was applied to the patient. Granulocyte colony-stimulating factor was added to the treatment because of neutropenia. Our case progressed rapidly after the first diagnosis, and chemotherapy continued in the 2nd postoperative month.

The authors certify that they have obtained all appropriate patient consent forms.

DISCUSSION

EWS/primitive neuroectodermal tumor (PNET) was described by Stout in 1918 and usually occurs as a sporadic aggressive malignant small round cell tumor in the soft tissues, bones, or central nervous system (1). It is examined under two main headings: central EWS/PNET, which develops from the central nervous system, and peripheral EWS/PNET, which grows out of the central nervous system (2). In this study, the tumor was of the peripheral type. This aggressive and unusual tumor has been seen in the esophagus, liver, pancreas, adrenal gland, kidneys,

prostate, bladder, and gynecological organs (3). Intestinal EWS may occur asymptomatically or present with fatigue and weakness due to the mass, as in our case, as well as symptoms such as intussusception (4), perforation (5,6), intestinal obstruction (7,8) and rupture.

The clinical presentation mainly depends on the affected area of the gastrointestinal tract. It may be misdiagnosed as a gynecological pathology, especially in young women, as the literature indicates that pain could often occur in the lower abdomen (9). Out of 38 reported cases, 3 originated in the esophagus, 9 in the stomach, 5 in the colorectal, and 20 in the small intestine. EWS, which included the primary omentum, was reported in only 2 cases. Twenty-two cases were observed in men, 15 cases were observed in women. Ewing sarcoma occurs in a wide age range from 9 to 68 years. There is no established treatment for intestinal PNET. Once diagnosed, surgical excision offers the best chance for survival, and adjuvant radiotherapy may reduce local recurrance (10). Combination chemotherapy traditionally includes vincristine, doxorubicin, cyclophosphamide, and dactinomycin. Adding ifosfamide and etoposide to a standard regimen significantly improves outcomes in patients with non-metastatic EWS (11). We chose multiagent chemotherapy because of the aggressive behavior of the tumor. Mesenteric PNET has a better prognosis than other regions independent of tumor size. In patients without metastasis, disease-free 5-year survival rate (>60%) is considerably higher than that in patients with metastatic disease (35%) (4). The reported causes of mortality were recurrent tumors in two patients, acute respiratory failure in one patient, and survival of the other two patients without any signs of disease. The reported follow-up period ranged from 6 to 20 months, with a median survival of 12 months.

Young women presenting with atypical clinical and imaging findings should be evaluated by a multidisciplinary approach during pre-, intra-, and post-operative periods for proper management of the disease.

ETHICS

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms.

Authorship Contributions

Surgical and Medical Practices: P.S.H., S.M., G.G., Concept: A.A., Design: G.G., Data Collection or Processing: G.G., Analysis or Interpretation: P.S.H., S.M., Literature Search: A.A., Writing: A.A.

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

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

REFERENCES

1. Mhawech-Fauceglia P, Herrmann F, Penetrante R, Beck A, Sait S, Block AM, et al. Diagnostic utility of FLI-1 monoclonal antibody and dual-colour, break-apart probe fluorescence in situ (FISH) analysis in Ewing's sarcoma/primitive neuroectodermal tumour (EWS/PNET). A comparative study with CD99 and FLI-1 polyclonal antibodies. Histopathology 2006;49:569-75.
2. Li T, Zhang F, Cao Y, Ning S, Bi Y, Xue W, et al. Primary Ewing's sarcoma/primitive neuroectodermal tumor of the ileum: A case report of a 16-year-old Chinese female and literature review. Diagn Pathol 2017;12:37.
3. Boehm R, Till H, Landes J, Schmid I, Joppich I. Ileoileal intussusception caused by a Ewing sarcoma tumour. An unusual case report. Eur J Pediatr Surg 2003;13:272-5.
4. Marec-Bérard P, Chotel F, Claude L. Tumeurs PNET/Ewing : prise en charge actuelle et perspectives [PNET/Ewing tumours: current treatments and future perspectives]. Bull Cancer 2010;97:707-13.
5. Horie Y, Kato M. Peripheral primitive neuroectodermal tumor of the small bowel mesentery: a case showing perforation at the onset. Pathol Int 2000;50:398-403.
6. Kim DW, Chang HJ, Jeong JY, Lim SB, Lee JS, Hong EK, et al. Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET) of the small bowel: a rare cause of intestinal obstruction. Int J Color Dis 2007;22:1137-8.
7. Sethi B, Smith GT. Primary primitive neuroectodermal tumor arising in the small bowel. Histopathology 2007;50:665-6.
8. Vignali M, Zacchè MM, Messori P, Natale A, Busacca M. Ewing's sarcoma of the small intestine misdiagnosed as a voluminous pedunculated uterine leiomyoma. Eur J Obstet Gynecol Reprod Biol 2012;162:234-5.
9. Yagnik VD, Dawka S. Extraskeletal Ewing's sarcoma/peripheral primitive neuroectodermal tumor of the small bowel presenting with gastrointestinal perforation. Clin Exp Gastroenterol 2019;12:279-85.
10. Grier HE, Krailo MD, Tarbell NJ, Link MP, Fryer CJ, Pritchard DJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003;348:694-701.
11. Bala M, Maly A, Remo N, Gimmon Z, Almogy G. Peripheral primitive neuroectodermal tumor of bowel mesentery in adults. Isr Med Assoc J 2006;8:515-6.