ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 4 | Volume: 17 | Year: 2021

MEDICAL JOURNAL OF BAKIRKÖY

www.bakirkoytip.org

ISSN: 1305-9319 | e-ISSN: 1305-9327 | Number: 4 | Volume: 17 | Year: 2021

MEDICAL JOURNAL OF BAKIRKÖY

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

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

Medical Journal of Bakirköy is an open Access, free and peer-reviewed journal and indexed in ESCI, EMBASE, Scopus, EBSCO and ULAKBİM TR Dizin.

Instructions for Authors and publication policy is available on our website.

www.bakirkoytip.org

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülşah Özgül

Finance Coordinator
Sevinç Çakmak

Project Coordinators
Aysel Balta
Duygu Yıldırm
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Meltem Acar
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu

Research&Development
Nihan Karamanlı
Melisa Yiğitoğlu

Digital Marketing Specialist
Seher Altundemir

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Printing Date: December 2021
ISSN: 1305-9319 **E-ISSN:** 1305-9327
International scientific journal published quarterly.

Advisory Board

Advisory Board

Advisory Board

Advisory Board

Advisory Board

Advisory Board

Contents

Research

Contents

Contents

Case Report

Index

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:280-285
DOI: 10.4274/BMJ.galenos.2021.41636

Research

The Influence of Human Leukocyte Antigens in Graft Versus Host Disease and Survival After Hematopoietic Stem Cell Transplantation in Pediatric Patients with Leukemia

Lösemili Pediyatrik Hastalarda Hematopoetik Kök Hücre Transplantasyonu Sonrası Graft Versus Host Hastalığı ve Sağkalımda İnsan Lökosit Antijenlerinin Etkisi

Kürşat Özdilli[1,2], Fatma Savran Oğuz[2], Sema Anak[3], Yeliz Öğret[2], Hayriye Şentürk Çiftçi[2], Rüştü Oğuz[4], Mahmut Carin[5]

[1]Medipol University Faculty of Medicine, Department of Medical Biology, Istanbul, Turkey
[2]Istanbul University, Istanbul Faculty of Medicine, Department of Medical Biology, Istanbul,Turkey
[3]Medipol University Faculty of Medicine, Department of Pediatric Hematology, Istanbul, Turkey
[4]Istanbul Demiroğlu Bilim University, Gayrettepe Florence Nightingale Hospital, Tissue Typing and Immunogenetic Laboratory, Istanbul, Turkey
[5]Istinye University, Tissue Typing and Immunogenetic Laboratory, Istanbul,Turkey

ABSTRACT

Objective: Hematopoietic stem cell transplantation (HSCT) is an important therapy for hematological diseases. One of the most significant complications of HSCT is graft versus host disease (GVHD), and major histocompatibility complex (MHC) is well known to affect GVHD and graft rejection. This study aimed to examine the effect of human leukocyte antigens (HLA) on the incidence of GVHD development in patients with leukemia.

Methods: The association between HLA and GVHD formation was evaluated in 57 patients with HSCT with HLA-identical sibling donors, of whom 37 were boys and 20 were girls with a mean age of 10.11 years. All patients were diagnosed with leukemia; acute myeloid leukemia (n=33), acute lymphoblastic leukemia (n=15), and chronic myeloid leukemia (n=9). Transplantation pairs were worked for HLA-A, -B, -C, and -DRB1 alleles. Class I HLA antigens were investigated using Terasaki microlymphocytotoxicity, whereas class II HLA alleles with polymerase chain reaction - sequence-specific amplification method.

Results: The frequency of developing GVHD in patients with HSCT was found to be 17.5% (n=10). HLA-DRB1*04 allelic frequency [p=0.024, odds ratio (OR): 4.87] was found to be higher in patients who developed GVHD. However, the HLA-DRB1*11 allelic frequency (p=0.031, OR: 0.12) was lower in patients who developed GVHD compared to patients who did not develop GVHD. Furthermore, HLA-B38 (p=0.002) and HLA-B41 (p=0.002) antigens were found only in patients who developed GVHD. The frequencies of the HLA-A26 allele (p=0.12) and the HLA-DRB1*11 allele (p=0.037, OR: 4.0) were higher in patients with relapse after HSCT; however, the frequencies of the HLA-A2 allele (p=0.033, OR: 0.19) was lower in patients who relapsed after HSCT.

Conclusion: This study assessed the relationship of HLA class with GVHD, relapse, and survival in children after HSCT in pediatric patients with leukemia.

Keywords: HLA, GVHD, leukemia, HSCT

ÖZ

Amaç: Hematopoetik kök hücre nakli (HKHN), hematolojik hastalıklar için önemli bir tedavidir. HKHN'nin en önemli komplikasyonlarından biri, graft-versus-host hastalığıdır (GVHH) ve büyük doku uyumluluk kompleksinin (*major histocompatibility complex-MHC*) GVHH ve greft reddini

Address for Correspondence: Kürşat Özdilli, Medipol University, Faculty of Medicine, Department of Medical Biology, Istanbul Turkey, Istanbul University, Istanbul Faculty of Medicine, Department of Medical Biology, Istanbul, Turkey Phone: +90 542 316 45 76 E-mail: hayriyesenturk@gmail.com ORCID ID: orcid.org/0000-0002-7129-5024

Cite as: Özdilli K, Savran Oğuz F, Anak S, Öğret Y, Şentürk Çiftçi H, Oğuz R, Carin M. The Influence of Human Leukocyte Antigens in Graft Versus Host Disease and Survival After Hematopoietic Stem Cell Transplantation in Pediatric Patients with Leukemia. Med J Bakirkoy 2021;17:280-285

Received: 26.12.2020
Accepted: 19.11.2021

etkilediği iyi bilinmektedir. İnsan lökosit antijenleri (human leukocyte antigen - HLA) tipinin lösemili hastalarda GVHH insidansı üzerindeki etkisini incelemeyi amaçladık.

Gereç ve Yöntem: HLA uyumlu kardeş donörleri ile HKHN olan 57 hastada HLA ve akut, kronik GVHH oluşumu arasındaki ilişki değerlendirildi. Çalışmaya yaş ortalaması 10,11 olan 37 erkek ve 20 kız dahil edildi. Tüm hastaların tanıları; Akut myeloid lösemi (n=33), akut lenfoblastik lösemi (n=15), kronik myeloid lösemi (n=9) idi. Tüm nakil kardeş çiftleri HLA-A, -B, -C, -DRB1 allelleri için tiplendirildi. Sınıf I HLA antijenleri Terasaki mikrolenfositotoksisite kullanılarak saptandı ve sınıf II HLA allelleri polimeraz zincir reaksiyonu-diziye özgü primerler (polymerase chain reaction with specific primer sequence) yöntemi ile analiz edildi.

Bulgular: HKHN uygulanan hastalar arasında GVHH insidansı %17,5 (n=10) olarak bulundu. HLA-DRB1*04 allelik frekansı [p=0,024, risk oranı (OR): 4,87] GVHH gelişen hastalarda daha yüksekti. Bununla birlikte, HLA-DRB1*11 allelik frekansı (p=0,031, OR: 0,12), GVHH gelişen hastalarda, GVHH geliştirmeyen hastalara göre daha düşüktü. Ayrıca, HLA-B38 (p=0,002) ve HLA-B41 (p=0,002) antijenleri sadece GVHH gelişen hastalarda bulundu. HLA-A26 alelinin (p=0,12) ve HLA-DRB1*11 alelinin (p=0,037, OR: 4,0) frekansları daha yüksekken, HLA-A2 allelinin frekansları (p=0,033, OR: 0,19) HKHN sonrası nükseden hastalarda daha düşük olarak saptandı.

Sonuç: Bu çalışma, lösemili pediatrik hastalarda HKHN sonrası çocuklarda HLA sınıfının GVHH, relaps ve sağkalım ile ilişkisini değerlendiren çalışmadır.

Anahtar Kelimeler: HLA, GVHH, lösemi, HKHN

INTRODUCTION

The success of bone marrow transplantation and remission depends on the degree of histocompatibility of human leukocyte antigens (HLA) between the recipient and the donor in allogeneic transplantation. In a transplant, HLA and minor histocompatibility antigens from the transmitted organ or tissue are delivered to the recipient organism. Antigens that are not possessed by the recipient organism are recognized by the T lymphocytes of the recipient, which results in graft rejection (1).

All patients undergoing hematopoietic stem cell transplantation (HSCT) have the risk of developing graft versus host disease (GVHD) after graft placement. The following are the involved mechanisms in GVHD pathogenesis: 1. Initial disease treatment and transplant-condition chemoradiotherapy may be a risk factor for GVHD via HLA and non-HLA molecule up-regulation, 2. HLA differences between the patient and the donor may lead to GVHD via T-cell reactivity, and 3. Cytotoxic T lymphocyte activation arising from excessive cytokine release may lead to GVHD (2). GVHD is orchestrated by immunologic response cells within the bone marrow and hematopoietic stem cells, especially T lymphocytes. Even if both the recipient and the donor possess the same HLA composition, all allogeneic recipients are at risk of developing GVHD due to the existence of minor histocompatibility antigens. mHAs are polymorphic antigens that contribute independently to HLA. mHA-1 and mHA-2 antigens expressed on hematopoietic cells are recognized by alloreactive T-cells and lead to GVHD (2). Many studies showed that HLA antigens play a role in GVHD development (3,4). The risk of chronic GVHD was reported to be significantly higher if the recipient and donor pairs with HLA class I allele mismatch (5). Despite the attainment of compatibility among the HLA-A, -B, and -DR alleles, GVHD is still a major complication that can result in mortality and morbidity (5).

Some studies indicated a possible relationship between GVHD and HLA antigens. The compatibility of both classes of the major histocompatibility complex (MHC) decreases the rate of mortality associated with GVHD. According to Wing and colleagues (6), the compatibility of HLA-A and HLA-B (class I) is as significant as the compatibility of the HLA-DR alleles (class II) (6).

This study aimed to examine the influence of HLA antigens on GVHD incidence between patients with leukemia who had undergone transplantation from HLA-identical siblings.

METHODS

In 57 blood samples, class I HLA antigens were investigated using Terasaki microlymphocytotoxicity, whereas class II HLA alleles were analyzed with the polymerase chain reaction - specific primer sequence (PCR-SSP) method. In the serological method, lymphocytes were isolated, and a 144-well plate containing HLA-A and HLA-B antibodies was used (7). The presence of DRB gene domains in the DNA samples was assessed with the PCR-SSP "low resolution" method using 24 primer pairs. PCR products were subjected to 2% gel electrophoresis and visualized under UV light (8). This is a retrospective study from a thesis (03.19.2003). Therefore, this study was approved by The Administrative Board of Istanbul University Institute of Health, Istanbul University, Istanbul, Turkey.

Study Population

The association between HLA antigens and the occurrence of acute and chronic GVHD was evaluated in 57 patients with HSCT having HLA-identical sibling donors, of whom 37 were boys and 20 were girls with a mean age of 10.11 years. All patients had leukemia [acute myeloid leukemia (AML)

(n=33), acute lymphoblastic leukemia (ALL) (n=15), chronic myeloid leukemia (CML) (n=9)]. Patients with AML were treated with busulfan and cyclophosphamide. VP16 and TBI were given to ALL patients. Patients with CML received cyclophosphamide and busulfan.

Statistical Analysis

Windows Statistical Package for the Social Sciences version 21.0 was used for statistical calculations (IBM, USA). Continuous numerical (quantitative) values were given as mean ± standard deviation (SD) and categorical (nominal) values as a percentage (%). The associations between HLA antigens and GVHD and relapse incidence were performed using Chi-square or Fisher's Exact test. Odds ratios (OR) were also calculated. Survival was calculated using the Kaplan-Meier test. Comparison of survival curves between the groups was done by long rank test. Statistical significance was accepted when the p-value was <0.05.

RESULTS

Our study group, which underwent HSCT, consists of 57 patients. Of this group, 33 (57.89%) were diagnosed with AML, 15 with ALL (26.32), and 9 with CML (15.79%). Thirty-seven of the patients were male and 20 were female with a mean age of 10.11 years. The patient characteristics are summarized in Table 1. Additionally, 12 (52.2%) patients with AML, 6 (26.0%) with ALL, and 5 (21.8%) with CML died, whereas 21 (61.7%) patients with AML, 9 (26.5%) with ALL, and 4 (11.8%) with CML were alive. The distribution of survival after HSCT according to the diagnosis is shown in Table 2.

Between patients who underwent HSCT, the incidence of GVHD was found to be 17.5% (n=10). The overall incidence of relapse was 23.0% (n=13) (Table 3).

Table 1. Characteristic of patients

Patients	Frequency	%	Age of mean ± SD
N=57	-	-	10.11±4.05
Diagnosis			
AML	33	57.89	9.85±4.04
ALL	15	26.32	9.45±3.99
CML	9	15.79	10.03±4.01
Sex			
Female	20	64.91	9.30±4.08
Male	37	35.09	10.54±4.02

AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, CML: Chronic myeloid leukemia, SD: Standart deviation

The HLA-DRB1*04 allelic frequency [p=0.024, OR: 4.87, 95% confidence interval (CI): 1.139-20.874] was higher in patients who developed GVHD. However, the HLA-DRB1*11 allelic frequency (p=0.031, OR: 0.12, 95% CI: 0.015-1.077) was lower in patients who had developed GVHD compared to patients who did not develop GVHD. Furthermore, HLA-B38 (p=0.002) and HLA-B41 (p=0.002) antigens were only found in patients who developed GVHD (Table 4). The frequencies of the HLA-A26 antigen (p=0.012, OR: 7.00 95% CI: 1.300-37.400) and the HLA-DRB1*11 allele (p=0.037, OR: 4.00 95% CI: 1.030-15.400) were higher, whereas that of the HLA-A2 antigen (p=0.033, OR: 0.19, 95% CI: 0.038-0.970) was lower in patients with relapsed after HSCT. This study revealed that the HLA-B62 allele (p=0.005, OR: 0.80, 95% CI: 0.600-1.070) was only found in patients who had relapsed after HSCT (Table 4). Our study revealed that the survival rate after HSCT ranged from 1 to 144 months, with a five-year survival rate of 57.4%. The survival rate among the 34 living patients ranged from 12 to 144 months, and that among the 23 patients who died after HSCT ranged from 1 to 60 months (Figure 1a). The five-year survival rate in girls was f 62% and that in boys was 59% (Figure 1b). Twenty-one of the 33 patients with AML survived, and five-year survival was 63%.

Moreover, 9 out of 15 patients with ALL survived, and their five-year survival rate was 60%. Additionally, 4 out of 9 patients with CML survived, and their five-year survival rate was 37% (Figure 1c). The five-year survival rate of patients who developed GVHD was 48% and that in patients who had not developed GVHD was 58% (Figure 1d).

DISCUSSION

Conventional chemotherapy results in a good prognosis by curing 70% of pediatric patients with a diagnosis of low-risk

Table 2. Survival rates of patients after HSCT

Survival (n=57)	Diagnosis	n	Frequency %
Yes (n=34)	AML	21	61.7
	ALL	9	26.5
	CML	4	11.8
	TOTAL	34	100
No (n=23)	AML	12	52.2
	ALL	6	26.0
	CML	5	21.8
	TOTAL	23	100

HSCT: Hematopoietic stem cell transplantation, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, CML: Chronic myeloid leukemia

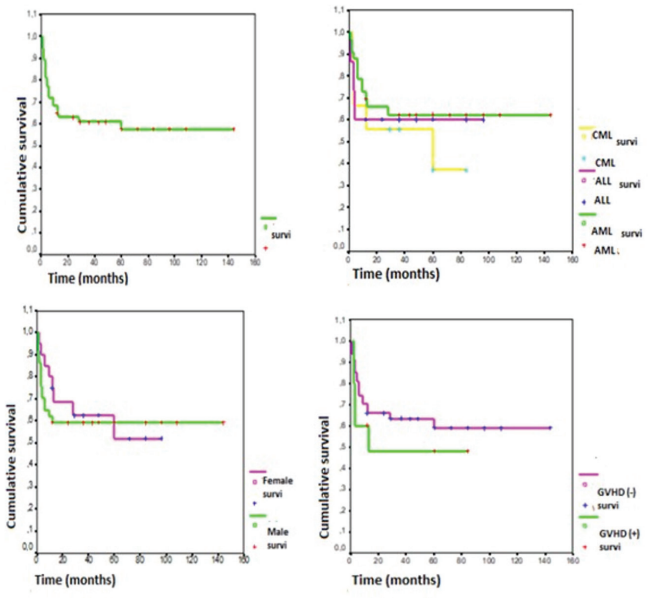

Figure 1. a. The survival rate, b. The survival rate according to diagnosis, c. The survival rate according to sex, d. The survival rate according to GVHD

GVHD: Graft versus host disease, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, CML: Chronic myeloid leukemia

ALL. In patients with high-risk ALL (chromosome anomaly, treatment responsiveness, and relapse), allogeneic SCT is a good therapeutic option (9). HSCT is an important therapy for hematological diseases (10,11). One of the most significant complications of HSCT is GVHD, and MHC is known to affect GVHD and graft rejection (12,13).

A study performed in 751 patients with CML who are transplanted from HLA-identical siblings revealed that HLA-A3 antigen was a risk for GVHD, whereas DR1 allele was shown to be protective against GVHD (2). A study by Kekik et al. (14) which was conducted in 108 adult patients who were transplanted with allogeneic bone marrow, reported that the HLA-A24 allele had a protective role against GVHD development. Kim et al. (15), who studied 389 patients in Korea, determined the acute GVDH rate after attention bias modification training (ABMT) as 34.8% and the chronic GVHD rate after ABMT as 21.2%. Additionally, patients with acute GVHD had a high frequency of HLA-B61 and HLA-Cw3; however, patients with chronic GVHD had a high frequency of HLA-B54. Another study revealed that the presence of the HLA-A10 (which is in the sub-group of HLA-A25 and HLA-A26) and HLA-B7 antigens were found to increase the risk of acute GVHD, whereas an increased frequency of HLA-B27 decreased the incidence of chronic GVHD (16). The number of patients who developed GVHD after HSCT (n=10) is low, thus previous research is insufficient on this

Table 3. GVHD and relapse rates after the HSCT

GVHD (+) (n=10),	17.5%	GVHD (-) (n=47)	82.5%
Survival	Frequency %	Survival	Frequency %
Yes (n=5)	(8.75%)*	Yes (n=29)	(50.91%)*
No (n=5)	(8.75%)*	No (n=18)	(31.59%)*
Sex			
Female (n=5)	(8.75%)*	Female (n=15)	(26.32%)*
Male (n=5)	(8.75%)*	Male (n=32)	(56.18%)*
Diagnosis			
ALL (n=2)	(3.5%)*	ALL (n=13)	(22.82%)*
AML (n=4)	(7.0%)*	AML (n=29)	(50.90%)*
CML (n=4)	(7.0%)*	CML (n=5)	(8.78%)*
Relapse (+) (n=13), 23.0%		Relapse (-) (n=44), 77.0%	
Survival	Frequency %	Survival	Frequency %
Yes (n=3)	(5.31%)*	Yes (n=31)	(54.25%)*
No (n=10)	(17.69%)*	No (n=13)	(22.75%)*
Sex			
Female (n=5)	(8.85%)*	Female (n=15)	(26.25%)*
Male (n=8)	(14.15%)*	Male (n=29)	(50.75%)*
Diagnosis			
ALL (n=3)	(5.31%)*	ALL (n=12)	(21.00%)*
AML (n=7)	(12.38%)*	AML (n=26)	(45.50%)*
CML (n=3)	(5.31%)*	CML (n=6)	(10.50%)*

*An in-group seen percentage, GVHD: Graft versus host disease, HSCT: Hematopoietic stem cell transplantation, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, CML: Chronic myeloid leukemia

subject. Cardozo and colleagues, who studied 179 patients, reported that acute GVHD is positively associated with HLA-A10, HLA-A26, B55, DRB1*15, and DQB1*05, whereas HLA-B16 is higher in patients without acute GVHD. Ivana and colleagues, who studied 96 patients, determined the acute GVDH rate after HSCT as 31.3% and the chronic GVHD rate after HSCT as 26.0%. Another study in patients carrying the HLA-A*01, DRB1*03, and DQB1*03 alleles revealed a statistically significantly lower ratio of acute GVHD, as well as the relationship with a higher ratio of chronic GVHD in patients carrying the HLA-DQB1*06 allele (18).

This study compared patients concerning the HLA haplotype, class I HLA-B antigens, namely HLA-B38 and HLA-B41, were not identified in patients who had not developed GVHD. Meanwhile, the frequencies of the class II HLA-DRB1 alleles, HLA-DRB1*04, and HLA-DRB1*11 were

Table 4. The relationship between HLA and GVHD, relapse

	GVHD (+) n=10		GVHD (-) n=47		p	OR CI%
HLA		%		%		
B38	2	20	0	0	0.002	0.80 (0.587-1.091)
B41	2	20	0	0	0.002	0.80 (0.587-1.091)
DRB1*04	5	50	8	17	0.024	4.87 (1.139-20.874)
DRB1*11	1	10	22	47	0.031	0.12 (0.015-1.077)
	Relapse (+) n=13		Relapse (-) n=44		p	OR, CI%
		%		%		
A2	2	17	23	51	0.033	0.19 (0.038-0.970)
A26	4	33	3	7	0.012	7.00 (1.300-37.400)
B62	2	17	0	0	0.005	0.80 (0.600-1.070)
DRB1*11	8	67	15	33	0.037	4.00 (1.030-15.400)

%: Within-group percentage [GVHD (+) / GVHD (-)], CI: Confidence interval, GVHD: Graft versus host disease, HLA: Human leukocyte antigens, OR: Odds ratio

higher and lower, respectively, in patients who developed GVHD compared to patients who did not develop GVHD.

Among 57 patients, 13 had relapsed (23.0%). The relapse frequency was higher in patients with AML (7/13). The comparison of patients with and without relapse revealed that, in patients with AML, the HLA-A26 frequency was higher but the HLA-A2 frequency was lower, which corroborates the idea of Von Fliedner et al. (19) that the presence of HLA-A2 is a sign of a good prognosis. Our study revealed that the HLA-DRB1*11 allelic frequency was higher in patients with relapsed HSCT, similar to previous studies that showed that the allelic frequency of this HLA is higher in patients with AML (19). Thus, a high frequency of the HLA-DRB1*11 allele could be a sign of a poor prognosis.

The rate of the HLA-A24 antigen was higher in patients who survived, whereas the frequencies of the HLA-A26 and HLA-B8 antigens were higher in patients who died after HSCT. HLA-A26 could be assessed as a bad prognosis factor because the HLA-A10 antigen increased the risk of acute GVHD and that the five-year survival rate of patients who developed GVHD is poor compared to that of patients who did not develop GVHD (16).

CONCLUSION

This study is very important since it evaluates the relationship of HLA class with GVHD, recurrence, and survival in children after HSCT. This study incorporated 57 cases from the genetic pool of the Turkish population, but larger studies must be performed in the future.

ETHICS

Ethics Committee Approval: This is a retrospective study from a thesis (03.19.2003). Therefore, this study was approved by The Administrative Board of Istanbul University Institute of Health, Istanbul University, Istanbul, Turkey.

Informed Consent: This is a retrospective study.

Authorship Contributions

Surgical and Medical Practices: K.Ö., S.A., Concept: K.Ö., F.S.O., Design: K.Ö., H.Ş.Ç., Data Collection or Processing: K.Ö., F.S.O., Analysis or Interpretation: K.Ö., F.S.O., Y.Ö., H.Ş.Ç., M.C., Literature Search: K.Ö., F.S.O., R.O., Writing: K.Ö., F.S.O., H.Ş.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. Roitt IM. Essential Immunology. London: Blackwell Science; 1997.
2. Clark RE, Hermans J, Madrigal A, Nachbaur D, Kropshofer G, Gratwohl A, et al. HLA-A3 increases and HLA-DR1 decreases the risk of acute graft-versus-host disease after HLA-matched sibling bone marrow transplantation for chronic myelogenous leukaemia. Br J Haematol 2001;114:36-41.
3. Askonas BA, Openshaw PJ. MHC and antijen presentation. Immunol Today 1989;10:396-7.
4. Long EO. Processing requirements for presentation of antigens to T lymphocytes. Curr Opin Immunol 1988;1:98-102.
5. Greinix HT, Faé I, Schneider B, Rosenmayr A, Mitterschiffthaler A, Pelzmann B, et al. Impact of HLA class I high-resolution mismatches on chronic graft-versus-host disease and survival of patients given hematopoietic stem cell grafts from unrelated donors. Bone Marrow Transplant 2005;35:57-62.

6. Leung WH, Turner V, Richardson SL, Benaim E, Hale G, Horwitz EM, et al. Effect of HLA class I or class II incompatibility in pediatric marrow transplantation from unrelated and related donors. Human Immunol 2001;62:399-407.
7. Terasaki PI, McClelland JD. Microdroplet assay of human serum cytotoxins. Nature 1964;204:998-1000.
8. Olerup O, Zetterquist H. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue Antigens 1992;39:225-35.
9. Jernberg AG, Remberger M, Ringden O, Winiarski J. Risk factors in pediatric stem cell transplantation for leukemia. Pediatr Transplant 2004;8:464-74.
10. Hoffbrand AV, Pettit JE. Acute Leukemias, Oxford, Blackwell Scientific Publications; 1993.
11. Lanzkowsky P. Bone Marrow Transplantation, New York: Churchill Livingstone; 1995.
12. Roitt I, Brostff J, Male D. Immunology. London: Mosby-Year Book; 1993.
13. Trowsdale J. Organization of the human MHC. In: Svejgaard A, Buus Soren, Fugger L, editors. HLA and Disease-the Molecular Basis. Alfred Benzon Symposium 40, Copenhagen; 1997. p. 21-32.
14. Kekik C, Besisik SK, Seyhun Y, Oguz FS, Sargin D, Carin MN. Relationship Between HLA Tissue Type, CMV Infection, and Acute Graft-vs-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation: Single-Center Experience. Transplant Proc 2009;41:3859-62.
15. Kim HJ, Park SJ, Im HW, Kim DW, Min WS, Kim HK, et al. The association of HLA antigen and GVHD in allogeneic hemopoietic stem cell transplantation with histocompatible sibling donor: a single-center experience in Korea. Int J Hematol 2002;76:267-71.
16. Remberger M, Persson U, Hauzenberger D, Ringden O. An association between human leucocyte antigen alleles and acute and chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation. Br J Haematol 2002;119:751-9.
17. Cardozo DM, Lieber SR, Marques SB, Aranha FJ, Vigorito AC, Souza CA, et al. Association between human leukocyte antigens and graft-versus-host diseases occurrence after allogenic hematopoietic stem cell transplantation. Sao Paula Med J 2012;130:219-24.
18. Ivana S, Bojtarova E, Kovacova M, Kluckova K, Kusikova M, Mistrik M, et al. Individual HLA alleles and risk of graft-versus-host diseases after haematopoietic stem cell transplantation from HLA-identical siblings. Biologia 2020;75:2045-52.
19. Von Fliedner VE, Sultan Khan Z, Jeannet M. HLA-A and HLA-B antigens in acute leukemia: A2--B12 phenotypes correlate with longer survival in acute myelogenous leukemia. Acta Haematol 1981;65:73-8.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:286-292
DOI: 10.4274/BMJ.galenos.2021.86158

Research

The Effects of Postpartum Education in Primipara Mothers on Their Readiness for Hospital Discharge and Maternal Self-confidence

Primipar Annelere Verilen Postpartum Eğitimin Taburculuğa Hazır Oluşluk Düzeyi ile Annelik Özgüvenine Etkisi

Betül Sönmez[1], Rojjin Mamuk[2]

[1]Dr. Burhan Nalbantoğlu State Hospital, Nicosia, North Cyprus
[2]Eastern Mediterranean University, Faculty of Sciences, Department of Nursing, Famagusta, North Cyprus

ABSTRACT

Objective: The postpartum period is one of the most critical periods of a woman. Thus, this study aimed to determine the effect of the postpartum education that is provided to mothers on the readiness for hospital discharge and maternal self-confidence.

Methods: This quasi-experimental study, with a non-random post-test control group, included all postpartum mothers who are hospitalized in a state hospital, including 102 primipara postpartum mothers (50 patients for the experimental group and 52 for the control group). Data were collected using a personal information form, Pharis self-confidence scale (PSCS), and Readiness for Hospital Discharge Scale-New Mother form (RHD-NMF). No intervention was made to the control group except for data collection. The experimental group took structured postpartum and neonatal care education and data were collected.

Results: The study showed that the experimental group's PSCS scores, the mean RHD-NMF total scores, and the RHD-NMF personal status, knowledge, and ability subscales were significantly higher than the control group ($p<0.05$). Furthermore, a significant positive correlation was determined between the two scales ($p<0.05$).

Conclusion: This study revealed that postpartum education supports mothers' readiness for hospital discharge and maternal self-confidence. Therefore, it should be routinely practiced in hospitals.

Keywords: Education, postpartum period, readiness for hospital discharge, self-confidence, women

ÖZ

Amaç: Doğum sonu dönem kadın yaşamının en kritik evrelerinden biridir. Bu çalışmada da doğum sonrası annelere verilen postpartum eğitimin taburculuğa hazır oluşluk düzeyi ile annelik özgüvenine etkisini belirlemek amaçlandı.

Gereç ve Yöntem: Çalışma yarı deneysel randomize olmayan gruplarda son test kontrol gruplu olarak tasarlandı. Çalışmanın evrenini bir devlet hastanesinde yatmakta olan lohusaların tamamı, örneklemini ise örneklem seçim kriterlerine uyan 102 (Deney 50/Kontrol 52) primipar lohusa oluşturdu. Verilerin toplanması aşamasında kişisel bilgi formu, Hastane Taburculuğuna Hazır Oluşluk Ölçeği-Yeni Doğum Yapmış Anne formu (HTHÖ-YDAF), pharis özgüven ölçeği (PÖÖ) kullanıldı. Kontrol grubuna veri toplama formlarının uygulanması haricinde herhangi bir müdahalede bulunulmadı. Deney grubuna ise yapılandırılmış Lohusalık ve Yenidoğan Bakımı Eğitimi verildikten sonra veri toplama araçları uygulandı.

Bulgular: Çalışmada PÖÖ puanları, HTHÖ-YDAF'nin toplam ortalama ölçek puanı ile HTHÖ-YDAF'nin kişisel durum, bilgi ve yetenek alt boyutlarının deney grubu; HTHÖ-YDAF'nin beklenen destek alt boyutunun ise kontrol grubu lehine anlamlı fark gösterdiği saptandı ($p<0,05$). Ayrıca iki ölçek puanları arasında istatistiksel olarak anlamlı ve pozitif yönde korelasyonlar olduğu tespit edildi ($p<0,05$).

Sonuç: Bu çalışma taburculuk öncesi verilen postpartum eğitimin, lohusaların taburculuğa hazır oluşluk düzeyi ile annelik özgüvenini olumlu yönde desteklediği ve bu nedenle hastanelerde rutin olarak uygulanması gerektiğini göstermektedir.

Anahtar Kelimeler: Eğitim, doğum sonu dönem, taburculuğa hazır oluşluk, kadınlar, özgüven

Address for Correspondence: Rojjin Mamuk, Eastern Mediterranean University, Faculty of Sciences, Department of Nursing, Famagusta, North Cyprus
Phone: +90 392 630 39 39 E-mail: rojinmamuk@gmail.com ORCID ID: orcid.org/0000-0003-3612-2010

Cite as: Sönmez B, Mamuk R. The Effects of Postpartum Education in Primipara Mothers on their Readiness for Hospital Discharge and Maternal Self-confidence. Med J Bakirkoy 2021;17:286-292

Received: 07.01.2021
Accepted: 19.11.2021

INTRODUCTION

The postpartum period is a critical term that involves several physical and psychosocial changes, as well as new roles and responsibilities. Thus, protecting and increasing both the mother's and the baby's health is critical (1,2). Today, most deliveries occur in the hospitals; however, postpartum care duration is very limited due to early discharge (3,4). The professional healthcare that is provided to families in the hospitals in the countries with postpartum home care and follow-up services is retained at home too, which makes postpartum early discharge advantageous for the family and health economy (3,5). However, this is not the case for countries that have no or insufficient prenatal training and consultancy services and postpartum home care (6,7).

Parental attitudes and behaviors are factors that affect the healthy growth and development of a baby (8,9). The parental self-confidence level is known to affect the attitudes and behaviors of parents (10-12). Nevertheless, physical changes during the early postpartum period, such as breastfeeding, bleeding, pain, and medical interventions if any, adaptation to motherhood, and parental self-confidence processes, occur (13,14). Studies showed a negative correlation between maternal self-confidence and stress, anxiety, and postpartum depression based on physical changes (15,16). Particularly, primipara, young mothers, mothers in the risky postpartum period, and those with premature babies need more support for information on self-care and baby-care (17,18). Therefore, training is organized that considers all mothers' skills, self-confidence, and support elements, especially those under risk information on self-care and baby-care (19,20).

Studies indicated that postpartum education and information affect mothers' readiness for hospital discharge (21-23) and maternal self-confidence (24-26). However, no study has searched for the relationship between readiness for hospital discharge after planned postpartum education and maternal self-confidence.

Aim

This study aimed to determine the effect of the postpartum education that is provided to mothers on the readiness for hospital discharge and maternal self-confidence.

Research Hypotheses

H_1: A difference is found between the scores of mothers who received and those who did not receive postpartum and neonatal care education from the readiness for hospital discharge scale-new mother form (RHD-NMF).

H_2: A difference is found between the scores of mothers who received and those who did not receive postpartum and neonatal care education from the Pharis self-confidence scale (PSCS).

H_3: A correlation is found between the scores of RHD-NMF and the PSCS.

METHODS

Study Design

This is a quasi-experimental study with a non-random post-test control group.

Participants and Setting

The study was conducted between May 1 and November 1, 2019, in a gynecology clinic in a public hospital in Northern Cyprus. As hospital protocol, hospital discharge was 24 h for non-risky postpartum and neonatal vaginal deliveries and 72 h for cesarean (C-section) deliveries. The hospital did not offer structured education for postpartum and neonatal care during pregnancy or postpartum period. The population of the study consisted of all postpartum mothers who are hospitalized in the gynecology clinics between the above-mentioned dates. Its impact size was calculated as d = 0.75, taking the total mean score that is obtained in the study of Burucu and Akın (21) as reference. With help of G*Power 3.1.9.2 software, the sample size that is needed for 95% power was 82 in total (41 in the experimental group and 41 in the control group). Considering potential drop-outs, the study was completed with 102 postpartum mothers (50 in the experimental and 50 in the control group). Additionally, the sampling criteria included primipara, postpartum mothers, over 18 years old, with Turkish literacy, no health problems of themselves or their babies, and are ready for discharge.

Data Collection Tools

The data were collected using personal information form, RHD-NMF, and PSCS.

Personal Information Form

The questionnaire was developed by the researcher, which included 18 questions regarding the mothers' socio-demographic, obstetric, and postpartum characteristics (21,27,28).

RHD-NMF

The validity and reliability study of the scale was developed to determine the postpartum mothers' early readiness for hospital discharge as conducted by Weiss et al. (29) in 2006 and Weiss and Piacentine (30). The validity and reliability of

the Turkish version were done by Akın and Şahingeri (27) This scale consisted of 4 subscales and 23 items in total. The first item was about the mother's readiness for planned discharge that is answered with a binary response (dichotomous) (yes/no) and was not included in the scoring. Other items were scored "0" to "10" by Likert-type scoring (27).

Items 2-9 were included in the first subscale (personal status). The third and sixth items were reverse scored. The second subscale (Knowledge) included items 10-16, the third subscale (Ability) included items 17-19, and the fourth subscale (expected support) included items 20-23. The lowest obtainable score was "0" the highest was "220." A higher score indicated higher readiness for hospital discharge, whereas lower scores indicated less readiness for hospital discharge. The scale was designed for hospital discharge. The Cronbach's Alpha value was 0.70 for its Turkish version (27). This value was found at 0.89 in the current study.

PSCS

The Turkish validity and reliability study of this scale that evaluates the self-confidence feelings of parents on daily maternal care was performed by Çalışır (28) with the reliability coefficient between 0.86 and 0.85. The PSCS is a five point-scale that consists of 13 items. Each baby-care item was scaled from 1 to 5 (none, few, partially, mostly, and completely). The lowest obtainable score from the scale was 13 and the highest was 65. A higher score indicated an increased self-confidence of parents about baby-care (28). The Cronbach's Alpha value was 0.94 in this study.

Education Plan Used in the Study

The education was planned at least postpartum 6 h for vaginal delivery and 24 h for C-section post-operation and takes approximately 60 min when mothers felt ready to receive an education. Education included follow-up of uterus involution and bleeding, perineum care, breastfeeding, drug use, postpartum risk symptoms, emergencies that require hospital admission, and contraception. Neonatal care education primarily included taking the baby on the lap, umbilical cord care, diaper change, baby bath, dressing the baby, and emergency hospital admissions. Furthermore, mothers were given a manual that was developed by the researchers. The manual, in addition to the above-mentioned issues, included postpartum physical and psychological changes, general hygiene, sleep and rest, time to begin intercourse, nutrition, newborn characteristics, screening programs, vaccination schedule, and contact addresses of health institutions and organizations that can be urgently referred.

The education plan and the manual were prepared according to the topics proposed by the Turkish Ministry of Health for pregnant patients (20). Before the pilot study, expert opinion and approval of four academics, midwives, and nurses were obtained. Education was supported by a demonstration using breast model, doll, bathtub, diapers, etc. materials. Patient rooms are not suitable for education, thus a room was reserved in the clinic to provide comfort for mothers and babies and use for education purposes.

Data Collection

The data of the control group were first collected to prevent interaction of the experimental and control groups. In the control group, pre-interview was made with mothers giving vaginal birth who are interviewed 6 h postpartum and mothers giving C-section interviewed 24 h post-operation. Participants were informed about the aim of the study before obtaining their consent and filling out the personal information form. Then, they filled out the RHD-NMF and PSCS before hospital discharge based on their statements. After the forms were filled, each mother was given an educational manual aside from the "postpartum and neonatal care education." However, no data were collected from this group regarding education.

A similar procedure took place for the data collected from the experimental group. After the personal information form was filled, postpartum and neonatal care education was given to mothers at a time when they felt ready and education manuals were distributed. Finally, they filled the RHD-NMF and PSCS based on their statements before hospital discharge. A pre-administration on 12 postpartum mothers was applied before the study. The study took its final shape based on the results. Cases that are included in the pre-administration were excluded.

Statistical Analyses

The statistical analyses were made using Statistical Package for the Social Sciences version 24.0. Data were analyzed using the chi-square test, and the adaptation of the scale scores to normal distribution was examined using the Kolmogorov-Smirnov test, Shapiro-Wilk test, and QQ plot graphic. The scale scores showed normal distribution, thus the groups were compared using an independent sample t-test. The correlations between RHD-NMF and PSCS scores were analyzed using the Pearson test. The significance level was found as p-values of <0.05. The study was approved by the Ethics Committee of Eastern Mediterranean University (ETK00-2019-0113, date: 26.04.2019). Additionally, the consent form following the Declaration of Helsinki was obtained from all participants.

RESULTS

The socio-demographic and obstetric characteristics of the groups are shown in Table 1. No difference was found in the socio-demographic and obstetric characteristics of the groups ($p>0.05$).

Table 2 shows the mothers' comparison of mean scores from the scales. The analyses indicated that the experimental group's PSCS and RHD-NMF total score and the scores from personal status, knowledge, and ability subscales were higher compared to the control group ($p<0.05$). However, the mothers' scores in the control group from the RHD-NMF expected support subscale were higher than those of the experimental group ($p<0.05$).

Table 3 shows the correlation analysis findings between the mothers' RHD-NMF and PSCS scores. Regardless of the experimental or control group, a positive significant correlation was found between the scores of mothers from the overall RHD-NMF, personal status, knowledge, and ability subscales, and PSCS scores ($p<0.05$). Additionally, the intergroup comparison found positive significant correlations between the scores of the experimental group from the overall RHD-NMF and knowledge subscale and the scores from PSCS ($p<0.05$). As for the control group, positive significant correlations were found between the mothers' scores from overall RHD-NMF, personal status, knowledge, and ability subscales, and PSCS scores ($p<0.05$).

DISCUSSION

The groups have similarities in socio-demographic and obstetric characteristics ($p>0.05$, Table 1). However, the readiness level of mothers in the experimental group who received an education was higher than those who did not receive education ($p<0.05$, Table 2). Similar studies that investigated the pregnancy and/or postpartum education or information showed that RHD-NMF total scale scores of the groups that receive education were higher than those who did not receive education (21,27,31-34). Another study showed no significant difference between the RHD-NMF total scale scores of mothers who received and who did not receive education; however, a significant difference was found between their RHD-NMF mean scores according to education subjects (35). Based on the samples from the literature and our study results, the postpartum period and discharge preparation increased the mothers' readiness for hospital discharge.

The statistical analysis showed a significant difference in favor of the experimental group regarding the RHD-NMF "personal status" subscale ($p<0.05$, Table 2). This finding supported the results of similar two studies (32-34). Contrarily, another study showed no difference between the groups in the personal status mean score (33). Samples from the literature and findings of this study indicated that postpartum and baby-care education increased mothers' physical welfare and readiness to return home after delivery.

The scores of the groups from RHD-NMF "Knowledge" and "Ability" subscales were compared and a statistical difference was found in favor of the experimental group ($p<0.05$, Table 2). Similar studies revealed that the mean scores of mothers in the education group from the knowledge and ability subscales were higher than those who did not receive education (32-34). Literature samples and our study results indicated that postpartum and baby-care education increased mothers' knowledge level and thus, their ability perception on the matter as intended.

Unlike other subscales and total scale scores, the "expected support" mean score was significantly higher in the control group ($p<0.05$, Table 2). Findings from similar studies differed from those obtained subscale results (32-34).

This study assessed the effects of postpartum and baby-care education on maternal self-confidence using PSCS and showed a significant difference in favor of the experimental group regarding mean score from the scale ($p<0.05$/Table 2). Similar studies found that the PSCS total mean score of mothers who received an education was higher compared to those who did not (24-26). Samples from the literature and our study results revealed that postpartum education is efficient in increasing maternal self-confidence.

The correlation between RHD-NMF and PSCS mean score was also analyzed in this study. As the mothers' scores from the overall RHD-NMF increased, the scores that are obtained from PSCS also increased ($p<0.05$, Table 3). This finding showed a positive correlation between the mothers' readiness for early hospital discharge and parental self-confidence. Therefore, postpartum and baby-care education, as in this study, can increase mothers' readiness for hospital discharge, thus their self-confidence in providing baby-care.

CONCLUSION

The postpartum and baby-care education provided to primipara postpartum mothers before hospital discharge increased the readiness level for hospital discharge and the scores of maternal self-confidence. Furthermore, a positive correlation was found between the two scales. Thus, the offered education possibly prepares the mothers for discharge and supports parental self-confidence.

Table 1. Comparison of mothers' socio-demographic and obstetric characteristics

	Experimental group (n=50)		Control group (n=52)		Total (n=102)		χ^2	p-value
	n	%	n	%	n	%		
Age	24.42±5.82		24.63±4.77		24.52±5.28			
21 years of age and below	19	38.00	14	26.92	33	32.35		
22–28 years of age	24	48.00	27	51.92	51	50.00	1.784	0.410
29 years of age and above	7	14.00	11	21.15	18	17.65		
Educational status								
Primary school	3	6.00	4	7.69	7	6.86		
Secondary school	20	40.00	19	36.54	39	38.24	0.225	0.974
High school	20	40.00	22	42.31	42	41.18		
University or higher	7	14.00	7	13.46	14	13.73		
Employment status								
Employed	18	36.00	23	44.23	41	40.20	0.718	0.397
Unemployed	32	64.00	29	55.77	61	59.80		
Family type								
Extended family	9	18.00	7	13.46	16	15.69	*1.37	0.518
Nuclear family	41	82.00	45	86.54	86	84.31		
Income status								
Less income than expense	20	40.00	13	25.00	33	32.35	*3.38	0.184
Equal income and expense	30	60.00	39	75.00	69	67.65		
Health insurance								
Yes	49	98.00	49	94.23	98	96.08	-	
No	1	2.00	3	5.77	4	3.92		
Number of pregnancy								
Once	46	92.00	46	88.46	92	90.20	-	
Two or more	4	8.00	6	11.54	10	9.8		
Number of abortion								
None	50	100.0	48	92.31	98	96.08	-	
One or more	0	0.00	5	9.61	5	4.9		
Planning pregnancy								
Planned pregnancy	45	90.00	49	94.23	94	92.16	-	
Unplanned pregnancy	5	10.00	3	5.77	8	7.84		
Receiving prenatal care								
Yes	49	98.00	52	100.0	101	99.02	-	
No	1	2.00	0	0.00	1	0.98		
Number of prenatal care								
9 and below	16	32.00	24	46.15	40	39.22		
Between 10 and 15	22	44.00	13	25.00	35	34.31	4,444	0.108
16 and above	11	22.00	15	28.85	26	25.49		

χ^2: Chi-square analysis *Fisher exact test was used. p>0.05

Table 2. Comparison of mothers' scores from readiness for hospital discharge scale-new mother form (RHD-NMF) and Pharis self-confidence scale (PSCS)

	Group	n	χ	s	*t	p-values
Personal status	Experiment	50	59.52	12.02	6,476	0.000**
	Control	52	44.52	11.38		
Information	Experiment	50	58.84	7.48	16,476	0.000**
	Control	52	27.02	11.52		
Ability	Experiment	50	25.26	3.81	6,840	0.000**
	Control	52	20.02	3.93		
Expected support	Experiment	50	14.62	7.70	-2,243	0.027**
	Control	52	17.85	6.82		
RHD-NMF Total	Experiment	50	158.24	20.92	10,959	0.000**
	Control	52	109.40	23.92		
	Group	n		s	Z*	p
Pharis Self-Confidence Scale	Experiment	50	60.30	4.33	18,335	0.000**
	Control	52	37.50	7.70		

*Unpaired t-test was used, **p<0.05, RHD-NMF: Readiness for hospital discharge scale-new mother form

Table 3. Correlation between the mothers' scores from the readiness for hospital discharge scale-new mother (RHD-NMF) and Pharis self-confidence scale (PSCS)

Experiment		Pharis Self-confidence scale		
		Control	Total	
Personal status	r*	0.172	0.294	0.573
	p	0.233	0.034**	0.000**
Information	r*	0.461	0.545	0.880
	p	0.001**	0.000**	0.000**
Ability	r*	0.105	0.299	0.584
	p	0.467	0.032**	0.000**
Expected support	r*	0.175	-0.100	-0.190
	p	0.223	0.480	0.055
Readiness for discharge	r*	0.347	0.423	0.774
	p	0.014**	0.002**	0.000**

*The Pearson correlation test was used, **p<0.05

ACKNOWLEDGMENTS

This study was generated from a postgraduate thesis that was completed at the Eastern Mediterranean University. Additionally, the authors would like to thank all the study participants and the staff in the gynecological diseases and delivery clinic.

ETHICS

Ethics Committee Approval: The study was approved by the Ethics Committee of Eastern Mediterranean University (ETK00-2019-0113, date: 26.04.2019).

Informed Consent: Participants were informed about the aim of the study before obtaining their consent and filling out the personal information form.

Authorship Contributions

Surgical and Medical Practices: B.S., Concept: B.S., R.M., Design: B.S., R.M., Data Collection or Processing: B.S., Analysis or Interpretation: B.S., R.M., Literature Search: B.S., R.M., Writing: B.S., R.M.

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. Fahey JO, Shenassa E. Understanding and meeting the needs of women in the postpartum period: The perinatal maternal health promotion model. J Midwifery Womens Health 2013;58:613-21.
2. Martínez-Galiano JM, Hernández-Martínez A, Rodríguez-Almagro J, Delgado-Rodríguez M, Rubio-Alvarez A, Gómez-Salgado J. Women's quality of life at 6 weeks postpartum: Influence of the discomfort present in the puerperium. Int J Environ Res Public Health 2019;16:1-9.
3. Gölbaşı Z. Early Postpartum Discharge Home Care Services and Nursing. Cumhuriyet Nursing Journal 2003;7:15-22.
4. Verpe H, Kjellevold M, Moe V, Smith L, Vannebo UT, Stormark KM, et al. Early postpartum discharge: maternal depression, breastfeeding habits and different follow-up strategies. Scand J Caring Sci 2019;33:85-92.
5. Yonemoto N, Dowswell T, Nagai S, Mori R. Schedules for home visits in the early postpartum period. Cochrane Database Syst Rev 2017:CD009326.

6. Tiruneh GT, Shiferaw CB, Worku A. Effectiveness and cost-effectiveness of home-based postpartum care on neonatal mortality and exclusive breastfeeding practice in low-and-middle-income countries: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2019;19:507.
7. Pallangyo TE, Mbekenga C, Olsson P, Eriksson L, Bergström A. Implementation of a facilitation intervention to improve postpartum care in a low-resource suburb of Dar es Salaam, Tanzania. Implement Sci 2018;13:102.
8. de Montigny F, Lacharite C. Fathers' perceptions of the immediate postpartal period. J Obstet Gynecol Neonatal Nurs 2004;33:328-39.
9. Ramchandani P, Stein A, Evans J, O'Connor TG; ALSPAC study team. Paternal depression in the postnatal period and child development: a prospective population study. Lancet 2005;365:2201-5.
10. Fasanghari M, Kordi M, Asgharipour N. Effect of maternal role training program based on Mercer theory on maternal self-confidence of primiparous women with unplanned pregnancy. J Educ Health Promot 2019;8:1-8.
11. Jones TL, Prinz RJ. Potential roles of parental self-efficacy in parent and child adjustment: A review. Clin Psychol Rev 2005;25:341-63.
12. Reece SM, Harkless G. Self-efficacy, stress, and parental adaptation: Applications to the care of childbearing families. J Fam Nurs 1998;4:198-215.
13. Finlayson K, Crossland N, Bonet M, Downe S. What matters to women in the postnatal period: A meta-synthesis of qualitative studies. PLoS One 2020;15:e0231415.
14. Hammes T, Sebold LF, Kempfer SS, Girondi JBR. Nursing care in postpartum adaptation: perceptions of Brazilian mothers. Journal of Nursing Education and Practice 2014;4:125-33.
15. Leahy-Warren P, McCarthy G, Corcoran P. Postnatal depression in first-time mothers: Prevalence and relationships between functional and structural social support at 6 and 12 weeks postpartum. Arch Psychiatr Nurs 2011;25:174-84.
16. Slomian J, Honvo G, Emonts P, Reginster JY, Bruyère O. Consequences of maternal postpartum depression: A systematic review of maternal and infant outcomes. Womens Health (Lond) 2019;15. https:// doi: 10.1177/1745506519844044.
17. Bora Güneş, N. Anxiety and Depression Levels of Mothers who have Premature Babies. Hacettepe University. Graduated School of Health Sciences, Pediatric Nursing Program, Doctoral Thesis; 2018.
18. Tan A, Pelone F, Arnold S, Anderson J, Kennedy G, Goodman J. Support and information needs of parents and carers of preterm babies requiring respiratory support on the neonatal unit: A qualitative systematic review. J Neonatal Nurs 2020;26:93-100.
19. Dol J, Campbell-Yeo M, Tomblin Murphy G, Aston M, McMillan D, Gahagan J, et al. Parent-targeted postnatal educational interventions in low and middle-income countries: A scoping review and critical analysis. Int J Nurs Stud 2019;94:60-73.
20. Republic of Turkey Ministry of Health. Post-partum care management guide. Available from: https://khgmsaglikhizmetleridb.saglik.gov.tr/TR,42925/dogum-sonu-bakimyonetim-rehberi. Accesssion date: 12.11.2019.
21. Burucu R, Akın B. Effect of Education Administered to Pregnants in Third Trimester on Level of Readiness for Postpartum Discharge. Journal of Hacettepe University Facultiy of Nursing 2017;4:25-35.
22. Kaya Şenol D, Aydın Özkan S, Hotun Şahin N. An investigation of postpartum mothers' readiness for hospital discharge and the affecting factors. Journal of Human Sciences 2017;14:1484-91.
23. Maldonado GM, Connelly CD, Bush RA. Predictors of readiness for hospital discharge after birth: Building evidence for practice. Worldviews Evid Based Nurs 2017;14:118-27.
24. Öztürk S, Erci B. The effect of training provided the primiparas in the postpartum period for motherhood and neonatal care on maternal self-confidence. Gümüşhane University Journal of Health Sciences 2016;5:25-31.
25. Balaban E. The effect of training of mothers of premature infants in neonatal intensive care unit on mother's self-confidence. Marmara University Health Sciences Institute Master Thesis 2016.
26. Batman D. Şeker S. Effect of web based education which has been applied to parents of premature infants to anxiety and self-confidence. DEUHFED 2019;2:107-15.
27. Akın B, Şahingeri M. Validity and Reliability of Turkish Version of Readiness for Hospital Discharge Scale–New Mother Form (RHD-NMF). Journal of Anatolia Nursing and Health Sciences 2010;13:7-14.
28. Çalışır H. The examination of the factors that affect the maternal role attainment of first-time mothers. Doctoral Thesis. Ege University Health Sciences Institute; 2003.
29. Weiss ME, Ryan P, Lokken L. Validity andrelialibility of the perceived readiness for discharge after birth scale. J Obstet Gynecol Neonatal Nurs 2006;35:34-45.
30. Weiss ME, Piacentine LB. Psychometric properties of the readiness for hospital discharge scale. J Nurs Meas 2006;14:163-80.
31. Altuntuğ K, Ege E. Effects of health education on mothers' readiness for postpartum discharge from hospital, on postpartum complaints, and quality of life. Hemşirelikte Araştırma Geliştirme Dergisi 2013;15:45-56.
32. Dağ H, Dönmez S, Şen E, Şirin A. Postpartum discharge readiness situation of women who had vaginal deliveries. Eur J Ther 2013;19:65-70.
33. Güleç T, Çoban A. The effect of discharging of cesarean postpartum discharge training on the readiness of the mothers to the discharge. J Health Sci Res 2019;6:461-9.
34. Şanar PS, Demirci H. Evolvotion of the planned education programme given to the mothers of the puerpera school named "Healty generations by the concious mothers". J Biotechnol and Strategic Health Res 2018;2:174-81.
35. Türkmen H. Özbaşaran F. Examination of status of readiness for hospital discharge among puerperant women who gave vaginal delivery. Journal of Duzce University Health Sciences Institute 2017;7:24-9.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:293-297
DOI: 10.4274/BMJ.galenos.2021.03521

Research

The Effect of Grape Seed Extract on the Pancreatic Weight in Diabetic Rats

Diyabetik Sıçanlarda Üzüm Çekirdeği Ekstresinin Pankreas Ağırlığına Etkisi

Elif Gülbahçe Mutlu[1], Emine Arslan[2], Hilal Arıkoğlu[3], Salih Varol[4]

[1]KTO Karatay University Faculty of Medicine, Department of Medical Biology, Konya, Turkey
[2]Selçuk University Faculty of Science, Department of Biology, Konya, Turkey
[3]Selçuk University Faculty of Medicine, Department of Medical Biology, Konya, Turkey
[4]KTO Karatay University Faculty of Medicine, Department of Physiology, Konya, Turkey

ABSTRACT

Objective: The pancreas is a vital organ that produces metabolic hormones and enzymes. Type II diabetes either arises from defective insulin secretion from pancreatic beta-cell cells or a diminished pancreatic beta-cell mass. The possible effects of grape seed extract on various metabolic diseases have been investigated in recent years. This study was designed to determine the effect of grape seed extract therapy on pancreatic mass.

Methods: Twenty-five rats were partitioned in five groups: control, diabetes and treatment groups in which was administered 100, 200, and 400 mg/kg of the grape seed extract, respectively. Regarding the origin of diabetic rats, 35 mg/kg of STZ was injected intraperitoneally into the diabetic control and treatment groups. The grape seed extract was administered to the treatment groups via gavage per the indicated doses (100, 200, and 400 mg/kg extract) for 28 days. All rats were dispatched post treatment. After dispatching the rodents, their pancreatic masses were obtainedand noted. Data analysis was performed in order to determine the differences between groups using the Statistical Package for Social Sciences version 22-SPSS (IBM Statistics 22).

Results: The pancreatic mass in diabetic rats was significantly ($p<0.05$) lower relative to the control rats. Equally, the pancreatic increased significantly in every treatment group compared to the control and diabetic groups ($p<0.05$). This increase was highest with the 400 mg/kg extract dose.

Conclusion: Grape seed extracts might be effective reversing pancreatic insufficiency in STZ-diabetic rats.

Keywords: Experimental diabetes mellitus, grape seed extract, pancreas, streptozotocin

ÖZ

Amaç: Pankreas metabolik hormonlar ve enzimler üreten hayati bir organdır. Tip II diyabet, pankreatik beta hücre hücrelerinden insülin sekresyonundaki bir başarısızlıktan veya pankreatik beta hücre kütlesindeki bir azalmadan kaynaklanır. Üzüm çekirdeği ekstresinin çeşitli metabolik hastalıklar üzerindeki olası etkileri de son yıllarda araştırılmaktadır. Bu çalışma, üzüm çekirdeği ekstresi tedavisinin pankreas ağırlığı üzerindeki etkisini belirlemek için tasarlanmıştır.

Gereç ve Yöntem: Yirmi beş sıçan beş gruba ayrıldı: Sırasıyla 100, 200 ve 400 mg/kg ekstrakt uygulanan kontrol, diyabet ve tedavi grupları. Diyabetik sıçanlar oluşturmak için 35 mg/kg doz STZ diyabet kontrol ve tedavi gruplarına intraperitonal olarak enjekte edildi. Üzüm çekirdeği ekstresi 28 gün boyunca belirtilen dozlarda (100, 200 ve 400 mg/kg ekstrakt) gavaj yoluyla tedavi gruplarına verildi. Tüm sıçanlar tedavi sonrası sakrifiye edildi. Sekrifiye edildikten sonra pankreas ağırlıkları tartıldı ve not edildi. SPSS yazılımı (IBM Statistics 22) kullanılarak gruplar arasındaki farkları belirlemek için istatistiksel analizler yapıldı.

Sonuç: Diyabetik sıçanlarda pankreas ağırlığı, kontrol sıçanlarına göre anlamlı olarak daha düşüktü ($p<0,05$). Ayrıca pankreas ağırlığı kontrol ve diyabet gruplarına göre tüm tedavi gruplarında anlamlı olarak artmıştır ($p<0,05$). Bu artış, 400 mg/kg ekstrakt dozunda en yüksekti.

Sonuç: Üzüm çekirdeği ekstresi, STZ-diyabetik sıçanlarda pankreatik yetmezliği düzeltmede etkili olabilir.

Anahtar Kelimeler: Deneysel diabetes mellitus, üzüm çekirdeği ekstresi, pankreas, streptozotosin

Address for Correspondence: Elif Gülbahçe Mutlu, KTO Karatay University Faculty of Medicine, Department of Medical Biology, Konya, Turkey
Phone: +90 542 425 74 68 E-mail: elifgulbahcemutlu@gmail.com ORCID ID: orcid.org/0000-0003-2391-2152

Cite as: Gülbahçe Mutlu E, Arslan E, Arıkoğlu H, Varol S. The Effect of Grape Seed Extract on the Pancreatic Weight in Diabetic Rats. Med J Bakirkoy 2021;17:293-297

Received: 03.03.2021
Accepted: 01.11.2021

INTRODUCTION

The pancreas is a vital endocrine and exocrine organ that produces different hormones and enzymes (1). An altered function in this organ could directly influence the physiological functions of the body (2,3). Type II diabetes occurs when the pancreas is unable to meet the metabolic needs resulting either from a i pancreatic β-cells dysfunction of insulin production or decreased beta-cell mass (4,5). Diabetes is one of the prevalent non-communicable diseases globally. It is disease characterized by a chronic hyperglycemia. In recent times, the global prevalence of diabetes has been rising steadily. It is believed by the International Diabetes Federation that the total number of diabetic victims worldwide will be approximately 642 million (6).

Streptozotocin (STZ) is a biochemical agent obtained "*streptomycetes achromogenes*" exhibiting diabetogenic properties and widely used in the generation of experimentally induced diabetes in animals (7,8). It was first reported by Rakieten that STZ selectively affects β-cells in Langerhans islets and has a highly specific diabetogenic effect (9). Its initial effect constitutes inhibiting β-cell response to glucose (10), followed by permanent cell damage and loss of function (11).

Traditional insulin treatment is inadequate due to reasons such as supply, storage and side effects, especially in developing countries. Thus, in recent times, newly developed alternatives include the use of natural or synthetic antidiabetic agents (12,13). Also, herbal therapies have been used in the management of diabetes in various regions in our country, as a result scientific studies are being carried to investigate thee hypoglycemic properties of these medicinal herbs (12).

Grape seed was first extracted in France in 1951 and was initially found to have auxiliary effects with vitamin C (14). Grape seeds are an important source of antioxidants because they are rich in flavonoids like catechin, epicatechin, procyanidins, anthocyanins, gallic acid, and phenolics such as ellagic acid, as well as stilbenes such as resveratrol and piceid (15). It has been reported to have beneficial effects on insulin resistance or diabetes, which occurs due to a decrease in the antioxidant content of the body (16,17). Grape seeds have not been reported by any study to have any in vivo side effects till date. However, it has been used as a nutritional supplement in America and Europe for many years. In addition, grape seed is included in the GRAS (generally considered safe) category by the U.S. Food and Drug Administration. The recommended daily dose of grape seed is between 100 and 300 mg (18).

The aim of this study was to investigate the effect of grape seed extracts on the pancreatic mass of rats on a high-fat diet and induced with low-dose STZ.

METHODS

Preparation of Grape Seed Extract

In this study, the red Globe grape seed (Vitis vinifera L.) varieties were used. Grape seeds, which constitute the herbal agents of the study, were separated from the cluster and their seeds were extracted. These seeds were then washed and dried at room temperature on blotter paper. The dried grape seeds were crushed into the powdered form and later extracted using the Downey et al. (19) method. The crude extract obtained was weighed to calculate the extraction efficiency afterwhich it was then lyophilized. The lyophilized extract was later dissolved in distilled water at concentrations of 100 mg/kg, 200 mg/kg, and 400 mg/kg.

Creating Experimental Diabetic Animal Model

Ethical approval for this study was obtained from the Konya Necmettin Erbakan University Experimental Medical Research Ethics Committee and Application Center for this study (decision no: 2013/005). In this study, the Wistar-Albino race rats (8-12-week-old female) for the experiment. The experimental rodents were obtained from the Konya Necmettin Erbakan University Experimental Medical Research and Application Center. The ages and especially live weights of the subjects were provided to be similar. They were housed at 22oC±2oC, 12 hours in a dark and 12 hours in a lighted environment. Feed and water were provided as ad libitum. Blood samples were collected from rats that completed the adaptation phase, the fasting blood sugar levels and lipid profiles were determined. In animals with statistically similar lipid profiles ($p<0.05$), an experimental type II diabetes model was induced according to the Srinivasan et al. method (20). The rats used in this study were separated into five groups as follows; the control group, the diabetes group and treatment group with 100, 200, and 400 mg/kg extracts administerd respectively. In order to experimentally induce diabetes, 35 mg/kg dose of STZ was dissolved in citrate buffer (pH 4.5) and administered as an intraperitoneal injection to rats in the diabetes and treatment groups. After 72 hours, the caudal vein blood sugar levels of the rats were measured with the aid of an autoanalyzer (Biotecnica Instruments, BT3000 Plus, Italy). Following this measurement, rats above 300 mg/dL were considered diabetic and included in the study (20).

Applying the Extract to the Rats and Measuring Pancreatic Masses

The treatment group rats were given to extract in each experimental group (100 mg/kg, 200 mg/kg, and 400 mg/kg extract) at a specified dose of gavage once daily for 28 days. At the end of this period, animals were euthanized, pancreatic masses were obtained and noted.

Statistical Analysis

Data analysis was performed using the IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA) statistical software. Regarding descriptive statistics, the number of units (n), percent (%), mean±standard deviation (mean ± SD), median (25^{th}-75^{th} percentile) values were reported. The normality distribution of the data with respect to numerical variables was evaluated by Shapiro-Wilk normality test and Q-Q graphs. For normally distributed variables, group comparisons over time were performed using the two-way analysis of variance in repeated measurements, meanwhile, multiple comparisons were performed by use of the Tukey HSD test.

Comparisons of the mean between two groups was done by parametric Student's t-test and comparisons between more than two groups were obtained by the One-Way ANOVA test. The Duncan test was performed to evaluate the significant difference between the groups following obtention of statistically significant ANOVA results. $P<0.05$ value was considered statistically significant.

RESULT

Concerning the findings of this study, pancreatic weight was observed to be significantly lower in the diabetic rats (0.66±0.20) compared to the control rats (0.88±0.31) ($p<0.05$). In addition, pancreatic weight increased significantly in every treatment group relative to the control and diabetic groups ($p<0.05$). The greatest increase was obtained from the extract treated group being 400 mg/kg (1.32±0.16) (Figure 1).

DISCUSSION

Diabetes is a chronic metabolic disease characterized by high blood sugar levels, which, over time, could lead to severe cardiovascular, ocular, renal, and neurological damage. Type II diabetes is most common, and develops especially in adults with insulinoresistance or insulinopenia. Beta cell dysfunction in pancreatic islets is one of the major causes of diabetes (21). Various studies in patients with type II diabetes have revealed a 7%-22% reduction in pancreatic volume using ultrasound, CT, and MRI (22-24). Several

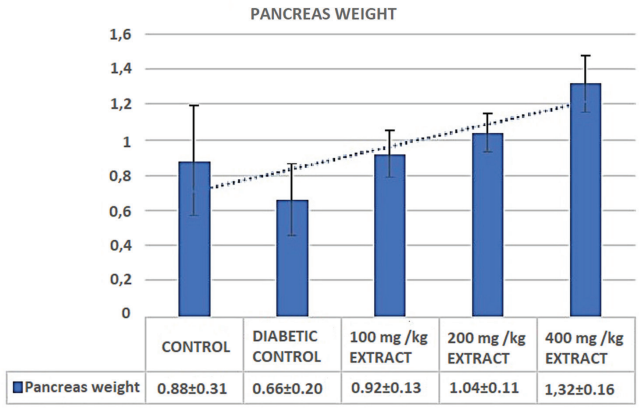

Figure 1. Average pancreatic weight change graphical illustration of experimental rats measured in five groups

studies have been conducted on the recovery of damaged pancreatic β-cells. In a study involving primates, a slight decrease in pancreatic volume was observed 2-6 months after inhibition of insulin secretion with low dose STZ (25). Against STZ-induced diabetic rats, "G. latifolium" and "O. gratissimum" leaf extracts were found to significantly reduce pancreatic weight (26). In another study, the effect of "M. alba" was investigated on β-cells in diabetic rats induced by STZ and revealed an increase in β-cells of groups treated with this plant (27). In addition, another group of researchers examined the effects of STZ-induced diabetes on the body weights of animals and the relative weights of the kidneys, liver, and pancreas. They disclosed that STZ-induced diabetes caused a significant decrease in body weight of diabetic animals, while the relative weights of kidney and liver increased but pancreatic weight was not affected (28). It has been revealed by many studies that a decrease in functional beta cell mass is a distinctive feature of type II diabetes.

It is clearly known in all living beings that cell density can be controlled in a variety of metabolic conditions to maintain a normal blood glucose level. Cells change dynamically in their functions and masses in response to insulin demand (29). Although it has been reported in many studies that both the size and number of islets in the pancreas of patients with type II diabetes have been reported (30-33) in this study, the pancreas of obese rats fed on a high-fat diet was weighed and an increase was observed in diabetic groups compared to control.

It has been reported in some studies that beta cell mass increases due to increased insulin resistance in obesity. Moreover, some studies have revealed that obese mice and rats experience a beta cell mass increase up to four times and a similar situation is observed in obese people, albeit

less (34-36). Despite the massive increase in obesity-related insulin requirement in obese people, this compensatory increase is thought to occur in the development of diabetes. Inadequate response to this condition is also believedt to be the underlying cause of hyperglycemia and the development of diabetes (37).

In vivo conditions, studies with animal models developed for pancreatic cell regeneration have been effective in setting molecular targets for stimulating cell growth or preventing pancreatic cell death. Loss of functional cells is a very important event in the development of diabetes. *In vivo* initiation of cell regeneration in the pancreas of diabetic patients seems to be one of the most convenient ways to eliminate the defective cell. For this reason, intensive studies have been performed and still ongoing to identify interactions between the cells in more detail to trigger cell proliferation and/or differentiation in *in vivo* conditions (38).

CONCLUSION

In this study, STZ was revealed to cause a decrease in the pancreatic mass of diabetic rats. Moreover, grape seed extract administration resulted in a significant rise in pancreatic mass. Considering other studies supporting this study, it can be concluded that grape seed extract protects pancreatic cells under hyperglycemic conditions and may be effective to correct pancreatic insufficiency in STZ-induced diabetic rats.

ACKNOWLEDGMENT

This study was approved by Selçuk University Scientific Research Projects with the grant number BAP /13201030.

ETHICS

Ethics Committee Approval: Ethical approval for this study was obtained from the Konya Necmettin Erbakan University Experimental Medical Research Ethics Committee and Application Center for this study (decision no: 2013/005).

Informed Consent: Patient consent was not obtained.

Authorship Contributions

Surgical and Medical Practices: E.G.M., E.A., H.A., Concept: E.A., H.A., Design: E.A., H.A., Data Collection or Processing: E.G.M., S.V., Analysis or Interpretation: E.G.M., S.V., Literature Search: E.G.M., S.V., Writing: E.G.M., S.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. Tiwari AK, Rao JM. Diabetes mellitus and multiple therapeutic approaches of phyto- chemicals: Present status and future prospects. Curr Sci 2002;83:30-8.
2. Hall JE. Secretory function of the alimentary tract. Guyton & Hall's textbook of medical physiology 2006;791-807.
3. Abd El-Haleem, Manal Reda; Mohamed, Dalia A. The effects of experimental aflatoxicosis on the pancreas of adult male albino rats and the role of ginger supplementation: a histological and biochemical study. Egyptian Journal of Histology 2011;34:423-35.
4. Burke JP, Williams K, Narayan KM, Leibson C, Haffner SM, Stern MP. A population perspective on diabetes prevention: whom should we target for preventing weight gain? Diabetes Care 2003;26:1999-2004.
5. Al-Qudah MM, Haddad MA, EL-Qudah JM. The effects of aqueous ginger extract on pancreas histology and on blood glucose in normal and alloxan monohydrate-induced diabetic rats. Biomed Res 2016;27:350-6.
6. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat Rev Endocrinol 2016;12:616-22.
7. Zusman I, Ornoy A, Yaffe P, Shafrir E. Effects of glucose and serum from streptozotocin-diabetic and nondiabetic rats on the in vitro development of preimplantation mouse embryos. Isr J Med Sci 1985;21:359-65.
8. Goud BJ, Dwarakanath V, Chikka B. Streptozotocin-a diabetogenic agent in animal models. Int J Pharm Pharm Res 2015;3:253-69.
9. Vardı N, Uçar M, Iraz M, Öztürk F. Deneysel diyabetin sıçan endokrin pankreasında oluşturduğu morfolojik değişiklikler. Turkiye Klinikleri J Med Sci 2003;23:27-32.
10. İrer SV, Alper G. Deneysel diyabet modelleri. Türk Klinik Biyokimya Derg 2004;2:127-36.
11. West E, Simon OR, Morrison EY. Streptozotocin alters pancreatic beta-cell responsiveness to glucose within six hours of injection into rats. West Indian Med J 1996;45:60-2.
12. Özbek H, Özgökçe F, Ceylan E, Taş A, Tunçtürk M. Secale cereale L. (Çavdar) Meyvesi Dekoksiyon Ekstresinin Sağlıklı ve Diyabetli Farelerde Hipoglisemik Etkisinin Araştırılması. Van Tıp Dergisi 2002;9:73-7.
13. Mıcılı SC, Özoğul C. Diyabette kök hücreler. Dokuz Eylül Üniversitesi Tıp Fakültesi Dergisi 2007;21:109-17.
14. Adamson GE, Lazarus SA, Mitchell AE, et al. HPLC method for the quantification of procyanidins in cocoa and chocolate samples and correlation to total antioxidant capacity. J Agric Food Chem 1999;47:4184-8.
15. Gürkan H. The importance of the throughout the history of vitis vinifera l. and its use today (Final project). Kayseri: Erciyes University; 2014.
16. Badavi M, Abedi H, Sarkaki A, Dianat M. Exercise Training and Grape Seed Extract Co-administration Improve Endothelial Dysfunction of Mesenteric Vascular Bed in STZ-induced Diabetic Rats. Int J Pharmol 2011;7:813-20.
17. Rostamian V, Shakeri F, Estakhr J. The Effect of Hydro-alcoholic Extract of Grape Seed (Vitis vinifera) on Sugar and Lipids in Serum of Diabetic Rats. Res J Biol Sci 2011;6:547-9.
18. Aşık G. Formaldehit maruziyeti sonucu sıçan testislerinde oluşan morfolojik değişiklikler üzerine üzüm çekirdeği ekstraktının (vitis vinifera) koruyucu etkisi (Yüksek Lisans Tezi). Balıkesir: Balıkesir Üniversitesi; 2016.
19. Downey MO, Mazza M, Krstic MP. Development of a stable extract for anthocyanins and flavonols from grape skin. Am J Enol Vitic 2007;58:358-64.

20. Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. Pharmacol Res 2005;52:313-20.
21. Yagihashi S. Advances in pathology of diabetes from pancreatic islets to neuropathy--a tribute to Paul Langerhans. Pathol Int 2015;65:157-69.
22. Alzaid A, Aideyan O, Nawaz S. The size of the pancreas in diabetes mellitus. Diabet Med 1993;10:759-63.
23. Goda K, Sasaki E, Nagata K, Fukai M, Ohsawa N, Hahafusa T. Pancreatic volume in type 1 and type 2 diabetes mellitus.Acta Diabetol 2001;38:145-49.
24. Burute N, Nisenbaum R, Jenkins DJ, Mirrahimi A, Anthwal S, Colak E, et al. Pancreas volume measurement in patients with Type 2 diabetes using magnetic resonance imaging-based planimetry. Pancreatology 2014;14:268-74.
25. Saisho Y, Manesso E, Butler AE, Galasso R, Kavanagh K, Flynn M, et al. Ongoing beta-cell turnover in adult nonhuman primates is not adaptively increased in streptozotocin-induced diabetes. Diabetes 2011;60:848-56.
26. Usoh IF, Akpanyuyng EO. Leaves extracts of Gongronema Latifolium and Ocimum Gratissimum offer synergy on organ weights alleviation and pancreatic resurgence against Streptozotocin diabetic rats. J Innov Pharmaceut Biol Sci 2015;2:522-36.
27. Mohammadi J, Naik PR. The histopathologic effects of Morus alba leaf extract on the pancreas of diabetic rats. Turk J Biol 2012;36:211-6.
28. Szkudelski T. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. Physiol Res 2001;50:537-46.
29. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH, et al. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab 2003;88:2300-8.
30. Wittingen J, Frey CF. Islet concentration in the head, body, tail and uncinate process of the pancreas. Ann Surg 1974;179:412-4.
31. Orci L, Malaisse-Lagae F, Amherdt M, Ravazzola M, Weisswange A, Dobbs R, et al. Cell contacts in human islets of Langerhans. J Clin Endocrinol Metab 1975;41:841-4.
32. Saito K, Takahashi T, Yaginuma N, Iwama N. Islet morphometry in the diabetic pancreas of man. Tohoku J Exp Med 1978;125:185-97.
33. Baetens D, Malaisse-Lagae F, Perrelet A, Orci L. Endocrine pancreas: three-dimensional reconstruction shows two types of islets of langerhans. Science 1979;206:1323-5.
34. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102-10.
35. Bouwens L, Rooman I. Regulation of pancreatic beta-cell mass. Physiol Rev 2005;85:1255-70.
36. Frayling TM. Genome-wide association studies provide new insights into type 2 diabetes aetiology. Nat Rev Genet 2007;8:657-62.
37. Mutlu EG. Tip II Diyabetik Ratlarda Vitis Vinifera L. Ekstraktının B-Katenin Geninin İfadesi Üzerine Etkisi (Doktora Tezi). Konya: Selçuk Üniversitesi; 2016.
38. Figeac F, Uzan B, Faro M, Chelali N, Portha B, Movassat J. Neonatal growth and regeneration of beta-cells are regulated by the Wnt/beta-catenin signaling in normal and diabetic rats. Am J Physiol Endocrinol Metab 2010;298:E245-56.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:298-303
DOI: 10.4274/BMJ.galenos.2021.82712

Research

Trendelenburg Lithotomy Position During Vaginoscopic Office Hysteroscopy Reduces Pain and Procedure Duration

Trendelenburg Litotomi Pozisyonu Vajinoskopik Ofis Histeroskopide Ağrıyı ve İşlem Süresini Azaltır

Fatma Ketenci Gencer[1], Semra Yüksel[1], Serkan Kumbasar[1], Bülent Babaoğlu[2], Berker Kavsi[3], Süleyman Salman[1]

[1]University of Health Sciences Hamidiye Medical Faculty, Gaziosmanpaşa Training and Research Hospital, Clinic of Gynecology and Obstetrics, Istanbul, Turkey
[2]Manisa Celal Bayar University Faculty of Medicine, Department of Gynecology and Obstetrics, Manisa, Turkey
[3]Bayrampaşa Kolan Hospital, Clinic of Obstetrics and Gynecology, Istanbul, Turkey

ABSTRACT

Objective: Vaginoscopic office hysteroscopy (VOH) is a gold standard diagnostic method for many uterine disorders. However, it may result in patient discomfort. This study aimed to investigate the effect of the Trendelenburg lithotomy (TL) position, in respect of the level of pain and procedure time during the VOH for diagnostic purposes.

Methods: This study included 157 patients between the ages of 20 and 65 years, of whom 74 underwent diagnostic VOH with the lithotomy position (group 1) and 83 with the TL position (group 2). Subsequent evaluation that was conducted on both groups included visual analog scale scores of patients, procedure duration, and the attitudinal Likert-type survey of doctors.

Results: A significant difference was found between groups 1 and 2 in pain scores ($p<0.001$), procedure duration ($p<0.001$), and attitudinal Likert-type survey of doctors ($p=0.002$). Group 2 reported lower pain scores than group 1 (3.34±2.37 and 5.69±2.33, respectively). Similarly, the procedure duration in group 2 was significantly reduced (60.11±26.3 and 83.3±29.5, respectively). The attitudinal Likert-type survey of doctors also showed significant improvement in group 2 (3.48±0.97 vs. 3.03±0.86, respectively).

Conclusion: VOH with the TL position lowered the pain scores in patients and reduced the procedure duration. The TL position is a good way of increasing the patients' compliance and tolerance. Likewise, it makes the procedure easier for the doctor without any additional price.

Keywords: Vaginoscopic office hysteroscopy, trendelenburg lithotomy position, procedure duration, pain, VAS

ÖZ

Amaç: Vajinoskopik ofis histeroskopi (VOH) uterin patolojilerin saptanmasında altın standart bir tanı yöntemidir fakat bu işlem hastaya rahatsızlık verebilir. Bu çalışmadaki amacımız tanı amaçlı yapılan VOH işleminde trendelenburg litotomi pozisyonunun ağrıya ve işlem süresine etkisini araştırmaktır.

Gereç ve Yöntem: Yaşları 20-65 yaş arasında değişen 157 hasta çalışmaya dahil edildi. Hastalardan 74'üne VOH işlemi litotomi pozisyonunda (grup 1) yapılırken, 83'üne trendelenburg litotomi (TL) pozisyonunda (grup 2) yapıldı. Her iki grupta hastalara vizüel analog skalası (VAS) uygulandı, işlem süresi kaydedildi ve doktorlara Likert tipi anket uygulanarak doktorların tutumları değerlendirildi.

Bulgular: Ağrı skorları ($p<0,001$), işlem süresi ($p<0,001$) ve doktorların Likert tipi anket sonuçları ($p=0,002$) açısından grup 1 ve grup 2 arasında anlamlı farklılık bulduk. Grup 2 hastaları, grup 1 hastalarına göre daha düşük ağrı skorları bildirdi (3,34±2,37, 5,69±2,33). Benzer şekilde grup 2'de işlem sırasında harcanan süre önemli ölçüde azaldı (60,11±26,3, 83,3±29,5). Doktorların Likert tipi ölçek sonuçlarında da grup 2'de önemli iyileşme gösterildi (3,48±0,97'ye karşı 3,03±0,86).

Sonuç: TL pozisyonuda VOH yapılması hastaların ağrı skorlarını düşürdü ve işlem süresini kısalttı. Üstelik hekimler için daha kolay olduğu görüldü. Poliklinik koşullarını VOH açısından optimize etmek için, hastaya TL pozisyonu vermek, hastaların uyumunu ve toleransını artırması bakımından iyi bir yoludur. Aynı şekilde herhangi bir ek maliyeti olmaksızın işlemi doktor için de kolaylaştırmaktadır.

Anahtar Kelimeler: Vajinoskopik ofis histeroskopi, trendelenburg litotomi, işlem süresi, ağrı, VAS

Address for Correspondence: Fatma Ketenci Gencer, University of Health Sciences Hamidiye Medical Faculty, Gaziosmanpaşa Health Application and Research Hospital, Clinic of Gynecology and Obstetrics, Istanbul, Turkey
Phone: +90 541 611 64 69 E-mail: fathma_k@hotmail.com ORCID ID: orcid.org/0000-0002-6076-2563

Cite as: Ketenci Gencer F, Yüksel S, Kumbasar S, Babaoğlu B, Kavsi B, Salman S. Trendelenburg Lithotomy Position during Vaginoscopic Office Hysteroscopy Reduces Pain and Procedure Duration. Med J Bakirkoy 2021;17:298-303

Received: 19.03.2021
Accepted: 19.11.2021

INTRODUCTION

Hysteroscopy has been a gold standard for evaluating the uterine cavity for the last four decades (1). "No-touch" vaginoscopic methods are getting more popular than the use of tenaculum or speculum with available equipment (2,3). Studies have shown that pain during the procedure is associated with the diameter of the hysteroscopy, the medium used, vaginal or oral misoprostol usage before the procedure, paracervical blocks, and bladder fullness (4). The most pain is felt during hysteroscopy with the passage through the cervical canal and endometrial biopsy taking (5). The circular cervical diameter is 4-6 mm in the nulliparous and 7-8 mm in the multiparous women (1). Hysteroscopy with an outer diameter of 5 mm and smaller can be used during the procedure. Still, the Bettocchi method allows the passage of the device through the canal without touching the cervical surface with a 30-degree angle optic and reduces the patients' pain (1,6).

Vaginoscopic office hysteroscopy (VOH) is a diagnostic method that is getting more popular in outpatient clinics. Despite its huge contribution to clinical practice, pain during the procedure is an important limiting factor (3). Maneuvers were investigated up to date to reduce pain during the procedure (4). However, research regarding the effectiveness of the position of the patient during the procedure is limited. With the additive effect of gravity, minor upside-down positioning of the patient, who is already in lithotomy position, may fasten and make the procedure easier. Therefore, this study aimed to elucidate the gap in the literature regarding the pain score and procedure duration during VOH for diagnostic purposes in the Trendelenburg lithotomy (TL) position for the first time. A randomized controlled trial was conducted to compare the pain score and procedure duration between the standard lithotomy position and TL position to gain scientific evidence. Additionally, the convenience for the physician performing the procedure was assessed.

METHODS

Our prospective randomized controlled study was conducted in University Taksim Traning and Research Hospital between November 2018 and April 2019. The study was approved by the institutional review board of Taksim Traning and Research Hospital (IRB number: 110/2018). Informed consent was signed by all patients before the procedure. The procedure and the possible complications were explained to the participants in detail. VOH procedure was performed by physicians with at least 3 years of experience. This study performed VOH solely for diagnostic purposes, thus no biopsy or any other surgical intervention was applied. VOH was performed in 157 patients aged 20-65 years. Pre-operative complete blood count, coagulation parameters (prothrombin time, activated partial thromboplastin time, and international normalized ratio) for hemorrhagic diathesis, and beta-human chorionic gonadotropin levels to exclude pregnancy were evaluated in all study participants before the treatment. The common indications for VOH include submucous fibroids, polyps, endometrial adhesion, and Mullerian anomaly. Patients with a history of cervical surgery, fibroids, or masses that narrow the cervical canal, pelvic infection, pregnancy, active bleeding during the procedure, and those with a retroverted uterus in ultrasonography were excluded. Hysteroscopy was performed in the mid-proliferative phase and patients were directed to urinate before the procedure.

The procedure duration was defined as the time that starts from the visualization of the vagina using a vaginoscope with saline, visualization of the cervical canal, endometrial cavity, and ends with both ostia. Neither speculum nor tenaculum was used during the procedure.

Patients were divided into two groups. Group 1 underwent a VOH procedure in the lithotomy position and group 2 was placed in the TL position, which is an upside-down position with a 30-degree angle (Figure 1).

A power analysis was performed to determine the number of participants, which revealed a minimum patient number of 64 with 80% power to detect a 30% difference in cases with an alpha value of 0.05. This study performed VOH in 74 patients in the lithotomy position and 83 patients in the TL position. The patient position was randomly selected by the nurse who prepare the patient according to the patient

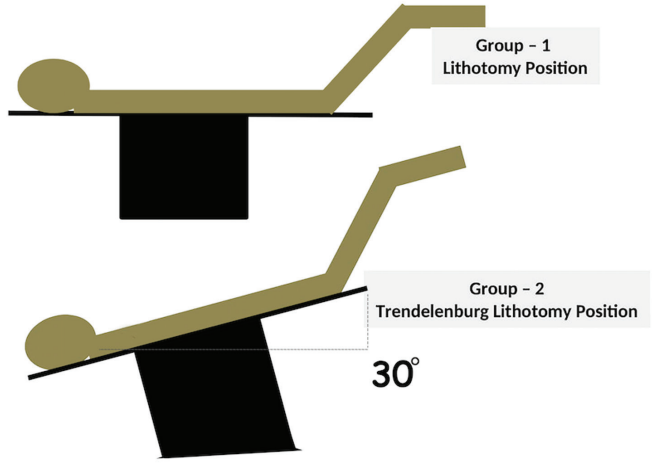

Figure 1. Positions that are preferred during office hysteroscopy. Normal lithotomy position was applied to patients in group 1, whereas 30° angulated TL position in group 2

protocol number in the hospital computer program. Patients with the protocol number that ended with an odd number were included in group 1 and the others were included in group 2. All patients were covered with drapes by the nurse before the doctors' arrival to avoid bias, but patients were allowed to watch the procedure from the screen. The procedure was performed using a 4 mm rigid (Olympus, Hamburg, Germany) hysteroscope with a 30-degree angle optic using a vaginoscopic (no touch) method without analgesia or anesthesia.

The visual analog scale (VAS) was used to evaluate pain levels with 0 that represents pain-free to 10 that described the most painful condition (6,7). Patients were asked to mark the pain expressing point on the VAS immediately after VOH. The pain severity is determined by the value of the point (cm) marked by the participant.

This study evaluated the convenience of the procedure by the physician with a 5-point attitudinal Likert-type survey, which is a psychometric scale that is commonly used to score responses in a questionnaire. The procedure ease or difficulty was categorized as 1: very easy; 2: easy; 3: ineffective; 4: difficult; and 5: very difficult, and the performing physician marked the appropriate section for each VOH procedure in the scale (8,9) (Figure 2).

Statistical Analysis

Statistical analysis of data was performed with the Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, USA). The Kolmogorov-Smirnov test was used to evaluate the distribution for normality. Non-parametric variables were compared with the Pearson chi-square test. The Student's t-test or Mann-Whitney U test was used to compare the parametric variables between groups 1 and 2. Power analysis was performed to determine the minimum sample size to perform the study with G-power (64 patients). P-values of <0.05 were considered statistically significant.

RESULTS

This study included 157 patients who applied to our outpatient clinic with different gynecological complaints. Among the participants, 5 patients were excluded from the study since VOH could not be performed due to vaginal reaction and cervical stenosis in 2 patients in the lithotomy and 3 in the TL position. A total of 74 patients underwent VOH (group 1) in the lithotomy and 83 in the TL position (group 2). The flow diagram was shown in Figure 1. Positional complications were not reported in any of our patients in both groups.

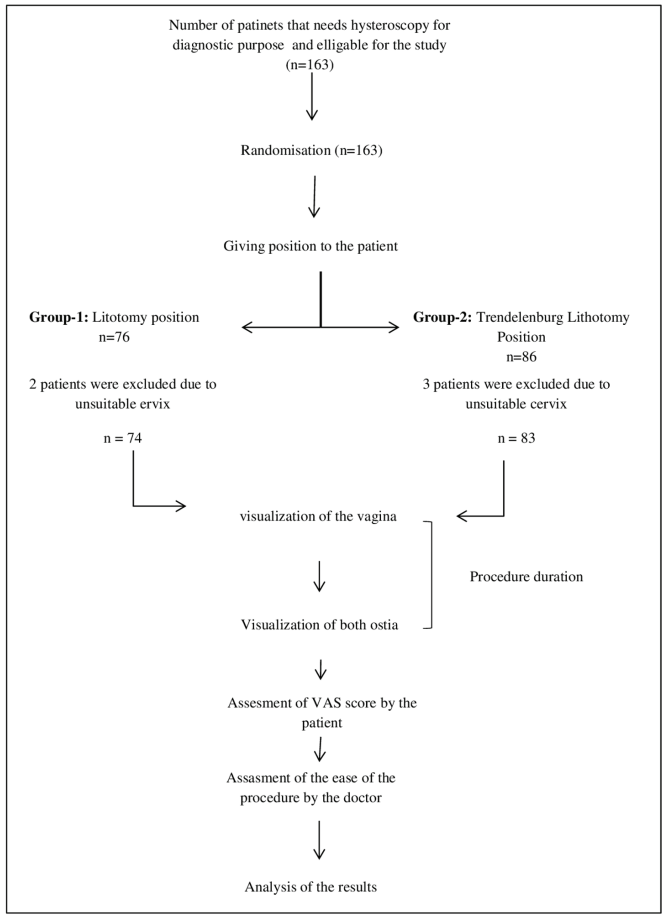

Figure 2. Flow diagram of the study protocol and patient enrollment
VAS: Visual analogue scale

The mean age of patients in group 1 was 41±8.5 years, whereas in group 2 was 42.3±10.2 years. No statistically significant difference was found between the two groups regarding patient age, gravidity, parity, number of abortions, number of curettages, body mass index, reproductive status, and type of delivery (Table 1). Of the total patients that underwent VOH, 66 (42.03%) had abnormal uterine bleeding, 16 (11.4%) had infertility, 47 (29.9%) had an endometrial polyp, 7 (4.4%) had submucous myoma, and 9 (5.73%) had other types of indications with no significant difference between the two groups (Table 1). The main findings throughout the whole procedure include endometrial polyp followed by normal cavity and other findings as shown in Table 1.

In group 1, the median VAS scores that were immediately recorded after the procedure was 5 (1-10), the procedure duration was 83.3±29.5 s, and the attitudinal survey of doctors was 3.48±0.97. In group 2, the median VAS score was 3 (0-9), the procedure duration was 60.11±26.3 s, and the attitudinal survey was 3.03±0.86. The pain level,

procedure duration, and attitudinal survey were statistically different between the groups (p<0.001, p<0.001, and p=0.002, respectively) (Table 1).

DISCUSSION

Our study revealed lower pain scores and shorter duration of hysteroscopy in TL position than lithotomy position during the procedure (p<0.001). Additionally, the doctor's attitude was evaluated using an attitudinal Likert-type survey during VOH for the first time and showed that the clinicians were more comfortable when patients were in TL position compared to standard lithotomy position (p=0.002).

Few studies investigated the maneuvers to reduce pain during diagnostic hysteroscopy. Maneuvers that provide uterine flattening, such as holding the cervix with the tenaculum, filling the bladder, filling the vagina with saline, suprapubic compression, gravity, and Trendelenburg position, facilitate the procedure, and authors compare these in the literature. Török et al. (10) investigated the effect of suprapubic pressure on pain during the procedure and cervical transit time and reported a significant reduction in cervical canal transit time but no effect on pain level. Similar to our study, uterine flattening was related to a shortened duration of the uterine entry. However, any effects were not

Table 1. Baseline characteristics of patients in each group

	Lithotomy group (group 1) (n=74)	**Trendelenburg group (group 2) (n=83)**	**p**
Age (years)	41±8.5	42.3±10.2	0.54*
BMI	70.1±11.9	69.2±12.3	0.64*
Gravidity	3 (0-9)	3 (0-9)	0.71**
Parity	2 (0-8)	2 (0-9)	0.70
Cesarean section only	19 (25.7%)	20 (24.1%)	0.81***
Any vaginal delivery	47 (63.5%)	55 (66.3%)	0.71
Postmenopausal women (n, %)	9 (12.2%)	17 (20.5%)	0.16
Hysteroscopy indications Abnormal uterine bleeding Submucous myoma Endometrial polyp Infertility Others	 37 (50%) 3 (4.1%) 24 (32.4%) 8 (10.8%) 2 (2.8%)	 29 (47%) 4 (4.8%) 23 (27.7%) 10 (12.0%) 7 (8.4%)	-
-	**Group 1: patients at lithotomy position (n=74)**	**Group 2: patients at Trendelenburg lithotomy position (n=83)**	**p**
Submucous myoma (%)	6 (8.1%)	6 (7.2%)	0.83
Undiagnosed (Luteal Phase) (%)	6 (8.1%)	7 (8.3%)	0.95
Synechia (%)	4 (5.5%)	2 (2.4%)	0.31
Normal cavity (%)	22 (30.1%)	30 (36.1%)	0.42
Endometrial polyp (%)	28 (37.8%)	32 (38.5%)	0.92
Mullerian anomaly (%)	3 (4.1%)	3 (3.6%)	0.88
Isthmocele (%)	5 (6.7%)	3 (3.6%)	0.37
-	**Lithotomy group (group 1) (n=74)**	**Trendelenburg group (group 2) (n=83)**	**p**
Procedure duration (seconds)	83.3±29.5	60.11±26.3	<0.001*
Pain estimated by the patient (VAS) †	5 (1-10)	3 (0-9)	<0.001**
Ease of hysteroscope insertion (Likert Score) §	3.03±0.86	3.48±0.97	0.002*

*Student's t-test **Mann-Whitney U-test ***Pearson Chi-square

Values were determined as n (%), mean ± SD, median (minimum-maximum)

†Visual analog scale was determined with a 10 cm scale pointed by the patient that represents the pain intensity

§Likert scale is an attitudinal type of survey to evaluate the convenience of the procedure

Values were determined as n (%), mean ± SD, median (minimum-maximum)

Pain means: 5.69±2.33, 3.34±2.37, SD: Standard deviation, BMI: Body mass index, VAS: Visual analogue scale

found on pain due to the application pressure and force on both the uterine and cervical canal. Our study revealed a positive effect of uterine flattening on pain reduction due to no further squeezed uterus with suprapubic pressure since we obtained a more flattened uterus by the effect of TL position, as well as the gravity. Additionally, the uterine filling is augmented, and the relatively heavier uterus becomes more flattened. Celik et al. (4) examined the effect of bladder distension and uterine flattening in diagnostic hysteroscopy that was performed using a tenaculum and revealed that bladder distension helps flattened uterus. Patients with bladder distension had lower pain scores and shorter procedure duration than patients with empty bladder during diagnostic hysteroscopy (4).

Our study applied up to a 30-degree Trendelenburg position in the procedures because it had been reported to reduce positional complications (e.g., cardiac output reduction, vital capacity, pulmonary compliance, tidal volume, minute volume decrease, congestive heart failure, pulmonary edema, facial, conjunctival, laryngeal, and tongue swelling, etc.). Additionally, advantages were also reported, such as decreased bleeding risk, facilitated surgical viewing distance, difficult trachea regurgitation, etc. (1,11).

The vaginal filling was effectively provided when the TL position was given to patients with an empty bladder. Thus, quick vaginal filling enables the medium to reach the optimum pressure force, which will dilate the cervical canal more quickly and effectively, leading to a more physiological dilatation before the cervical visualization than the lithotomy position. The medium does not overflow from the vagina by the effect of gravity until the vagina is filled, thus facilitating the full filling of the uterine cavity. With the effect of gravity on the relatively heavier uterus and TL position, uterine flattening is achieved. Therefore, easy entrance through a flat uterus improved the pain score of patients and shortened the duration of the procedure. Additionally, similar results were obtained in both studies because both were performed based on providing uterine flattening with simple techniques. In our method, the rapid vaginal filling with the medium by gravity facilitated image acquisition. We believe that when the patient can witness the vaginoscopic monitoring of cervical ostium, the tolerance and compliance increase, together with uterine flattening, which resulted in reduced pain scores and decreased procedure duration in the TL group. Contrarily, Fouda et al. (12) designed a study in a group of menopausal women and compared the effect of 400 mg vaginal misoprostol administration 12 h before the procedure and bladder straightening by instructing the patients to drink 1 l of water 2 h before the procedure to achieve bladder filling. They found that vaginal misoprostol administration was superior to bladder straightening for harboring pain management (12). The main determinant point in this study is that the menopausal woman has an extra narrow cervix due to hormonal status; therefore, cervical ripening due to misoprostol facilitated the entrance. Bladder straightening seemed insufficient because the cervix was more straightened but still narrow. Our study did not exclude the menopausal woman in both groups, thus the mean and the median of our main outcomes were still comparable even with the negative effect of patients who are menopausal. Main outcomes may improve in a group of non-menopausal women.

Many medical studies have used the Likert scale to achieve more scientific and accurate conclusions, particularly in subjective assessments. The Likert scale was used by Nandhini et al. (13) in a patient group administered with 200 mcg vaginal misoprostol 3 h before vaginoscopic hysteroscopy and a non-administered patient group and revealed that the procedure got easy and the complication was less in the misoprostol group. Nada et al. (14) applied 400 mcg of oral and vaginal misoprostol to patients 12 h before the operative hysteroscopy. Surgeons were evaluated on how easy the cervical dilatation was using a Likert scale and revealed that oral or vaginal administration did not affect the convenience of the surgeon. Likert scale setting and scoring technique in our study revealed that the doctors found the procedure easier when patients were in the TL position than the lithotomy position ($p=0.002$).

The comprehensive study by Kabli and Tulandi (15) revealed no difference for pain score when using a mixture of lidocaine and saline as a distending medium compared to only the saline used to group. Our study revealed lower visual pain scores in the TL group ($p<0.001$) without any analgesic agent administration, which can be useful if added to our method since the response of flattened uterus to analgesics during the VOH procedure was undetermined.

Karakuş et al. (16) compared the effectiveness of local anesthesia methods for analgesia in diagnostic hysteroscopy and demonstrated that patients with cervical spray application had less pain during tenaculum insertion compared to placebo. Additionally, intrauterine topical anesthesia reduced pain during and after the procedure (16). Tenaculum was not used in our vaginoscopic procedure. Thus, pain due to the tenaculum was ignored in both groups. Hence, we just assessed the pain while passing through the canal and visualizing the cavity. Pain scores and procedure duration might be further reduced with local or intrauterine topical anesthesia in the TL group.

De Angelis et al. (17) revealed that the application of a subcutaneous electrical nerve stimulation device in-office hysteroscopy was associated with lower pain. Maybe, a combination of this non-invasive method with ours improves pain scores and shortens the procedure duration.

Study Limitations

Study limitations include the absence of a subgroup composed of menopausal women since the number of menopausal participants in each group is limited, thus their results are not comparable.

CONCLUSION

In light of these findings, hysteroscopy is a procedure that can be applied even in outpatient clinics. Many different applications and technical procedures have been tried to achieve optimal standards. This study revealed that performing VOH in TL position provided shorter procedure duration and lower pain scores. Additionally, the clinicians found the TL position more comfortable than the lithotomy position. Placing patients in a TL position is simple, cheap, and worth it since pain is still a limiting factor for VOH despite new feasible equipment. More studies that focus on combinations of our technique with others in the literature are needed to achieve a better and more qualified environment both for the patient and the operator during office hysteroscopy.

Ethics

Ethics Committee Approval: Our prospective randomized controlled study was conducted in University Taksim Traning and Research Hospital between November 2018 and April 2019. The study was approved by the institutional review board of Taksim Traning and Research Hospital (IRB number: 110/2018).

Informed Consent: Written consent was obtained from all patients before attending the study.

Authorship Contributions

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

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. Bettocchi S, Nappi L, Ceci O, Selvaggi L. What does 'diagnostic hysteroscopy' mean today? The role of the new techniques. Curr Opin Obstet Gynecol 2003;15:303-8.
2. Neves AR, Mairos J, Martino PD. How the Location of Intracavitary Lesions Influences Pain during Office Hysteroscopy. J Minim Invasive Gynecol 2019;26:1334-9.
3. Tagliaferri V, Ricciardi L, Ricciardi R, Pinto LR, Lanzone A, Scambia G, et al. Carbon dioxide in office diagnostic hysteroscopy: An open question. A multicenter randomized trial on 1982 procedures. Eur J Obstet Gynecol Reprod Biol 2019;235:97-101.
4. Celik C, Tasdemir N, Abali R, Bastu E, Akbaba E, Yucel SH. The effect of uterine straightening by bladder distention before outpatient hysteroscopy: a randomised clinical trial. Eur J Obstet Gynecol Reprod Biol 2014;180:89-92.
5. De Angelis C, Santoro G, Re ME, Nofroni I. Office hysteroscopy and compliance: mini-hysteroscopy versus traditional hysteroscopy in a randomized trial. Hum Reprod 2003;18:2441-5.
6. Ekin M, Yaşar Y, Akgöl S. Comparison of Vaginoscopic No Touch Method with The Traditional Method of Outpatient Hysteroscopy. Med J Bakirkoy 2009;5:63-6.
7. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45-56.
8. Şahin DB, Gülleroğlu HD. Examination of the psychometric properties of scale developed through item analysis techniques that are used to select items for Likert-type. Asian Journal of Instruction 2013;1:18-28.
9. Lınkert R. A Technique fort he Measurement of Attitudes. Archives of Psychology 1932;22:140-55.
10. Török P, Herman T, Lőrincz J, Molnár S, Lampé R, Póka R. Suprapubic pressure facilitates the procedure of office hysteroscopy: A randomized controlled trial. Obstet Gynaecol Res 2019;45:640-4.
11. Min JH, Lee SE, Lee HS, Chae YK, Lee YK, Kang Y, et al. The correlation between the Trendelenburg position and the stroke volume variation. Korean J Anesthesiol 2014;67:378-83.
12. Fouda UM, Elshaer HS, Elsetohy KA, Youssef MA. Misoprostol versus uterine straightening by bladder distension for pain relief in postmenopausal patients undergoing diagnostic office hysteroscopy: a randomised controlled non-inferiority trial. Eur J Obstet Gynecol Reprod Biol 2016;203:326-30.
13. Nandhini B, Maurya DK, Keepanasseril A, Kubera NS. Effect of cervical priming with misoprostol on cervical entry in women undergoing vaginoscopic hysteroscopy for evaluation of abnormal uterine bleeding: a randomized controlled trial. Arch Gynecol Obstet 2018;298:133-7.
14. Nada AM, Elzayat AR, Awad MH, Metwally AA, Taher AM, Ogila AI, et al. Cervical Priming by Vaginal or Oral Misoprostol Before Operative Hysteroscopy: A Double-Blind, Randomized Controlled Trial. J Minim Invasive Gynecol 2016;23:1107-12.
15. Kabli N, Tulandi T. A randomized trial of outpatient hysteroscopy with and without intrauterine anesthesia. J Minim Invasive Gynecol 2008;15:308-10.
16. Karakuş R, Namazov A, Ayas S, Polat M, Arınkan SA, Angın AD, et al. Efficacy of local anesthesia for office hysteroscopy. Zeynep Kamil Med J 2014;45:136-41.
17. De Angelis C, Perrone G, Santoro G, Nofroni I, Zichella L. Suppression of pelvic pain during hysteroscopy with a transcutaneous electrical nerve stimulation device. Fertil Steril 2003;79:1422-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:304-311
DOI: 10.4274/BMJ.galenos.2021.65487

Research

Retrospective Evaluation of Hospitalized Patients Treated with Pleural Drainage Due to Pleural Effusion

Hastanede Yatırılarak Tedavi Edilmiş ve Plevral Effüzyon Nedeniyle Plevral Drenaj Uygulanmış Hastaların Retrospektif Olarak Değerlendirilmesi

Servet Özdemir[1], Faruk Karandere[2], Necati Çıtak[1], Mustafa Özer Ulukan[3], Abdulbaki Kumbasar[2]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Thoracic Surgery, Istanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, Istanbul, Turkey
[3]Istanbul Medipol University Faculty of Medicine, Department of Cardiovascular Surgery, Istanbul, Turkey

ABSTRACT

Objective: Pleural effusion (PE) is a common pathological condition that can occur during the clinical course of many diseases. This study aimed to retrospectively evaluate the clinical features and treatment results of patients with pleural fluid drainage due to PE.

Methods: A retrospective analysis was performed in the study with 103 patients between January 2020 and March 2021, who had pleural drainage due to PE. The posteroanterior and lateral chest radiographs were evaluated.

Results: A total of 103 patients were included in the study, with an overall mean age of 62.5 years minimum: 24, maximum: 91 years. Most patients had three or more comorbid diseases (n=53, 51.5%). The majority of patients had drainage using a pleural catheter (n=97, 94.2%). Cytological examination of the pleural fluid revealed malignancy in 5 (4.9%) patients, whereas 89 (86.4%) were discharged during follow-up, and 14 (13.6%) had mortality. In the patients who died, more fluid with exudate characteristics at a level close to statistical significance was detected. Malignant cells were detected in the pleural fluid in 10% of patients with primary malignant cases (n=50), whereas no malignant cell was found in the pleural fluid of patients without malignancy diagnosis (n=53), with a statistically significant difference between patients with and without malignancy. The total length of hospital stay was significantly higher in patients undergoing a second surgical procedure.

Conclusion: Patients undergoing pleural fluid drainage had at least one systemic disease. The most common systemic disease in patients was a cardiac disease, followed by malignant disease. "No malignant cells were detected in the fluids of patients without primary malignancy," in the cytology. In addition, the rate of second pleural surgery is high in PE cases, which further prolongs the length of hospitalization of these patients.

Keywords: Pleural effusion, transudate-exudate, pleural catheter, pleural drainage, thoracentesis

ÖZ

Amaç: Plevral efüzyon (PE) birçok hastalığın klinik seyri sırasında ortaya çıkabilen ve sık görülebilen bir patolojik durumdur. Bu çalışmada, iç hastalıkları kliniğinde yatırılarak tedavi edilmiş ve PE nedeniyle plevral sıvı drenaj uygulanmış hastaların klinik özelliklerini ve tedavi sonuçlarını retrospektif olarak değerlendirmeyi amaçlanmıştır.

Gereç ve Yöntem: Çalışmada Ocak 2020 ile Mart 2021 tarihleri arasında iç hastalıkları kliniğinde yatırılarak tedavi edilmiş ve PE nedeniyle plevral drenaj uygulanmış 103 hasta geriye dönük olarak incelenmiştir. Bu hastalardaki mevcut komorbit hastalıklar kayıt edilmiştir. Bütün hastaların çekilmiş olan posteroanterior ve lateral akciğer grafileri incelenerek sıvı miktarları değerlendirildi. Olguların demografik özellikleri, sıvı analizinde dikkat çeken özellikleri, torasentez dışında kullanılan tanı yöntemleri, drenaj için kullanılan cerrahi yöntemler, işleme ait komplikasyonlar, hastaların yatış süresi ve sağkalım durumları değerlendirildi.

Bulgular: Hastaların yaş ortalaması 62,5 yıl minimum: 24, maksimum: 91 yıl idi. Yüz üç hastanın 58'i kadın (%56,3) ve 45'i erkekti (%43,7). Hastaların çoğunluğunda üç ve üzeri komorbidit hastalık mevcuttu (n=53, %51,5). Hastaların çoğunluğuna plevral katater ile drenaj uygulanmıştı (n=97, %94,2). Drenaj sonrasında hastaların %10,7'sinde (n=11) cerrahi girişime ait komplikasyon izlendi. Plevral sıvının sitolojik incelenmesinde hastaların beşinde (%4,9) plevral sıvıda maligniteye rastlandı. Toplam drenaj süresi ortalama 8,8 gün iken (min: 1 gün, maks: 68 gün, IQR=7) toplam hastanede kalış süresi 23,6 gün (min: 3, maks: 103, IQR=19) olarak hesaplandı. Takipte hastaların 89'u taburcu edilirken (%86,4), 14'ü

Address for Correspondence: Servet Özdemir, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Thoracic Surgery, Istanbul, Turkey
Phone: +90 505 357 24 34 E-mail: servetozdemir74@hotmail.com ORCID ID: orcid.org/0000-0002-8458-0772

Cite as: Özdemir S, Karandere F, Çıtak N, Ulukan MÖ, Kumbasar A. Retrospective Evaluation of Hospitalized Patients Treated with Pleural Drainage Due to Pleural Effusion. Med J Bakirkoy 2021;17:304-311

Received: 24.04.2021
Accepted: 16.10.2021

eks olmuştu (%13,6). Eksitus olan hastalarda istatistiksel anlamlılığa yakın düzeyde daha fazla eksüda vasfında sıvı saptandı. Primer malignitesi mevcut olan hastaların (n=50) %10'unda plevral sıvıda malign hücre saptanırken malignite tanısı olmayan hastaların (n=53) hiçbirinde plevral sıvıda malign hücre saptanmamıştı ve bu aradaki fark istatistiksel olarak anlamlıydı (p=0,02). İkinci kez cerrahi girişim gerektiren hastalarda hastanede kalış süresi anlamlı olarak yüksek bulundu.

Sonuç: Pleral sıvı drenajı uygulanmış hastalarda en az bir sistemik hastalık mevcuttu. Hastalarda en sık görülen sistemik hastalık kardiyak hastalıklarken ikinci sırada ise malignansiler yer almaktadır. Drenaj sonrası komplikasyon görülebilmekte ancak majör komplikasyon gelişmemektedir. Mortaliteyi etkileyen faktörler sıklıkla hastaya ait olan primer sistemik hastalığa bağlıydı. Primer maligniteye sahip olmayan hastalarda plevral sıvının sitolojik incelemesinde malign hücreye rastlanmadı. Ayrıca PE'lerde ikinci plevral cerrahi işlem oranı yüksektir bu durum hastaların yatış süresini daha da uzatmaktadır.

Anahtar Kelimeler: Plevral effüzyon, transüda-eksüda, plevral katater, plevral drenaj, torasentez

INTRODUCTION

An abnormal amount of fluid between the parietal and the visceral pleura is expressed as pleural effusion (PE) (1). PEs may occur as a result of increased fluid release in the pleural space or decreased pleural fluid absorption. PEs are frequent conditions (2). The frequency of determining PE is accepted as 4/1,000 people per year (3). That is, PE can be seen in many diseases rather than a single disease caused by pathologies that disrupt the formation and absorption mechanism of the pleural fluid (4-6).

Differential diagnosis in PE includes a wide spectrum, patient evaluation requires a systematic approach, and systemic diseases must be considered (7). Almost all systemic pathologies, such as the cardiovascular, gastrointestinal, endocrine, and genitourinary systems, and connective tissue can cause PE. Anamnesis and clinical examination of a patient with PE can guide the physician to determine if the PE is exudative or transudative. This significant distinction may also scale down the differential diagnosis and guide further research (4). Congestive heart failure is the most common cause of transudative PE. Contrarily, connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, often cause exudative PE.

All these evaluations reduce unnecessary invasive procedures and shorten the time for diagnosis (8). If deemed as appropriate, the process continues with thoracentesis, and the pleural fluid that is collected is analyzed. As necessary, other examinations and procedures, such as thorax computed tomography (CT), thorax ultrasonography, magnetic resonance, and positron emission tomography/CT pleural biopsy, as well as video-assisted thoracoscopy (VATS), and bronchoscopy, can be added (9).

This retrospective study aimed to investigate the clinical status of 103 patients with PE who had pleural drainage in the department of internal medicine and evaluate its compliance with the literature.

METHODS

Before the research, approval for the study was obtained from the Ethics committee of the University of Health Sciences Turkey, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2021/96). In addition, informed consent for the patient's information was obtained from the patient(s) or a legally authorized representative before hospitalization.

This study retrospectively examined 3,768 patients hospitalized at the University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital-Internal Medicine Clinic between January 2020 and March 2021. PE was determined in 347 (9.2%) of these patients. Posteroanterior (PA) and lateral chest radiographs obtained at admission were examined. Considering the PA radiography, the pleural fluid amount was defined as minimal (fluid covering the costophrenic angle, not covering the entire diaphragm), moderate (fluid covering <2/3 of the hilus), and massive (fluid covering >2/3 of the hemithorax). Drainage is applied in patients with moderate and massive PE (Figures 1 and 2) in the hospital; however, drainage is not inserted in patients with minimal PE (Figure 3), except for the presence of exudative fluid. Drainage is not inserted as the first option according to the hospital procedure, except for a radiological appearance in stable respiratory and

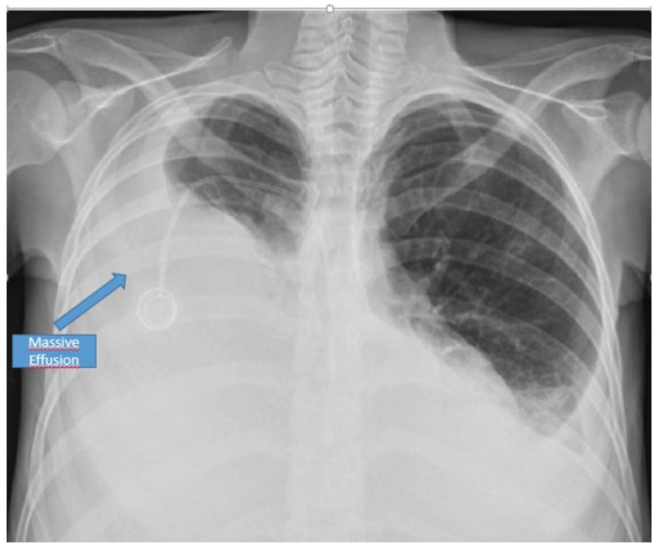

Figure 1. X-ray massive PE compromising the right pleural cavity
PE: Pleural effusion

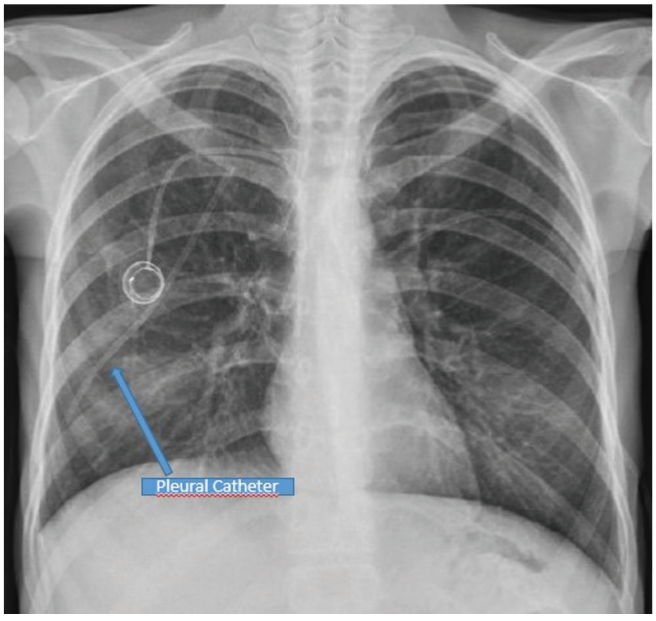

Figure 2. X-ray of the pleural cavity of figure 2 after pleural drainage with pleural catheter

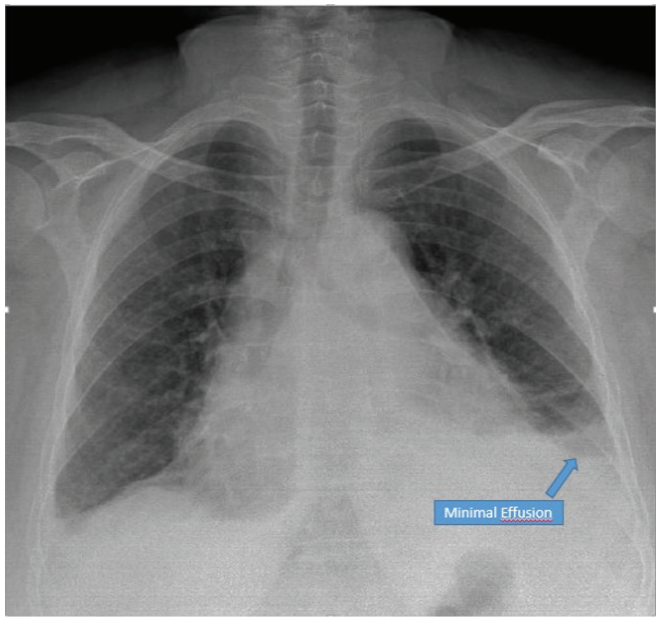

Figure 3. X-ray of minimal pleural effusion at the left costophrenic sinus indicated by arrow

hemodynamic parameters of patients with minimal PE and no deterioration in the patient's clinical course. Taking all these into consideration, 103 patients undergoing pleural drainage due to moderate and massive PE, were included in the study. These 103 patients comprise 2.7% of a total of 3,768 cases and 29.6% of 347 cases with PE.

Before the pleural catheter insertion in patients with PE, thoracentesis was performed, and the macroscopic appearance of the fluid sample was evaluated. The pleural catheter was inserted (8-10 Fr) in patients with serous PE. Chest drainage tube insertion (28-32 Fr) was performed for patients with a dark consistency and dense cell (empyema, chylothorax, and hemothorax). In the follow-up, the pleural catheter or chest tube was removed when the amount of pleural drainage was <100 cc/day and when the chest X-ray radiography showed regression in the fluid and expansion in the lungs after drainage.

During the procedure, data on age, gender, demographic characteristics, the underlying cause of PE, comorbidities, characteristics of pleural fluid, surgical procedure, and complications during or after the surgical procedure were collected from the patient file and recorded in a previously prepared data collection form. The pleural fluid location was classified as unilateral (right or left hemothorax) or bilateral.

Comorbid diseases were grouped as cardiac, pulmonary, renal, diabetes mellitus (DM), and malignancy. Patients with coronary artery disease, congestive heart failure, hypertension, and cardiac arrhythmia were evaluated as the cardiac disease group. Patients with chronic obstructive pulmonary disease, asthma, bronchial, pneumonia, TBC, and pulmonary embolism were grouped as pulmonary disease groups. Conditions, such as chronic renal failure, acute renal failure, and kidney transplant history, were classified as renal disease. Patients diagnosed with DM before admission were included in the DM group. All patients with primary malignancy who are diagnosed before hospitalization were included in the malignant disease group. In addition, each patient may have more than one comorbidity, the number of comorbidities was divided into three subgroups as one, two, three, or more.

The drugs (such as anticoagulants) that the patient was using and those constituted a relative contraindication for surgical intervention were recorded.

All cases included in the study were differentiated as transudative or exudative based on the Light criteria with a biochemical examination in the fluid sample taken before the treatment. If one or more of the specified criteria were present, the fluid was considered to be exudate: 1) pleural fluid/serum protein of >0.5; 2) pleural fluid/serum lactate dehydrogenase (LDH) of >0.6; and 3) pleural fluid LDH higher than 2/3 of the upper limit of serum LDH's optimal laboratory values (8). In the absence of any of these criteria, pleural fluid was defined as transudative. The fluid samples collected from all patients were sent to pathology for cytological malignancy examination.

After the first drainage, the pleural drainage catheter was removed in patients who were thought to be treated both medically and surgically. However, some patients required the second drainage due to pleural fluid recurrence. For

patients who received drainage for the second time, pleural drainage duration and length of hospital stay (LOS) were recorded. Whether the patients were discharged or died during the hospitalization were examined.

Statistical Analysis

The data were entered into the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA) software package. Descriptive statistics were used to summarize pertinent study information. Quantitative variables were presented as mean, maximum (max), and minimum (min) values and qualitative variables were presented as percentage values. Normal distributions were tested and reported as mean values. The Student's t-test was used for comparisons between groups. Pearson's chi-squared test was used for qualitative variable analyses; however, Fisher's Exact test was used if the sample size was small. Non-parametric continuous variables, presented as median values, were compared using the Mann-Whitney U test. Statistical significance was set at a p-value of <0.05.

RESULTS

The mean age of patients was 62.5 years [min: 24, max: 91 years, Interquartile range (IQR): 27.0], wherein 58 were female (56.3%) and 45 were male (43.7%). The conditions of the patients in terms of anticoagulant drug use, number of comorbidities, and subtypes of comorbidities were shown in Table 1. Most patients had three or more comorbid diseases (n=53, 51.5%). The most common comorbidities were found in the cardiac diseases group (n=60, 58.3%), followed by malignant diseases group (n=50, 48.5%). PE was detected on the right side in 63 patients and on the left side in 32 patients, whereas bilateral in the remaining 8 patients (Table 1).

Most patients had drainage using a pleural catheter (n=97, 94.2%), whereas the remaining were drained by tube thoracostomy, and 1 was drained by VATS. Following the surgical procedures, complications related to the procedure were observed in 10.7% (n=11) of patients. The most common complication was pneumothorax (n=10), whereas 1 patient developed an intrathoracic hematoma.

Considering the PE type, the transudative rate was 52.4%, whereas the exudative rate was 47.6% (Table 2). As a result of pathological examinations, malignancy was found in the pleural fluid in 5 of all patients (4.9%). The total drainage time was 8.8 days (min: 1 day, max: 68 days, IQR: 7) on average, whereas the total LOS was calculated as 23.6 days (min: 3, max: 103, IQR: 19).

Regarding PE types, a significant difference between patients with transudative and exudative fluid in terms of malignancy (p=0.04) and pulmonary disease (p=0.009) was found (Table 2). Exudative fluid was mostly observed in patients with cancer (59.2% vs. 38.9%), whereas transudative fluid was more likely observed in pulmonary disease (31.5% vs. 10.2%). A difference close to significance was also found in terms of pleurisy (p=0.06). Exudative fluid was observed to be mostly bilateral, but transudative one was more left-sided. No significant difference was found between the groups in terms of other variables.

During the follow-up, 89 of patients (86.4%) were discharged and 14 of them died (13.6%). No statistical difference

Table 1. Demographic and clinical characteristics of patients

Variables	Data
Age, year ± SD	62.5±16.7
Sex, n (%)	
Male	45 (43.7%)
Female	58 (56.3%)
Anticoagulant drug use, n (%)	12 (11.7%)
Number of comorbidities, n (%)	
1	33 (32.0%)
2	17 (16.5%)
3 or more	53 (51.5%)
Malignancy presence, n (%)	50 (48.5%)
DM, n (%)	30 (29.1%)
Cardiac disease group, n (%)	60 (58.3%)
Renal disease group, n (%)	27 (26.2%)
Pulmonary disease group, n (%)	22 (21.4%)
Pleural effusion side, n (%)	
L	32 (31.1%)
R	63 (61.2%)
Bilateral	8 (7.8%)
The type of surgical intervention performed first, n (%)	
Pleural catheter	97 (94.2%)
Tube thoracostomy	5 (4.9%)
VATS	1 (1.0%)
Surgery-related complication, n (%)	11 (10.7%)
Type of the pleural effusion, n (%)	
Transudate	54 (52.4%)
Exudate	49 (47.6%)
Malignancy detection in pleural fluid, n (%)	5 (4.9%)
Duration of drainage, day ± SD	8.8±8.4
Need for a second surgical procedure at hospitalization, n (%)	31 (30.1%)
Situation, n (%)	
Discharge	89 (86.4%)
Mortality	14 (13.6%)
Length of hospitalization, day ± SD	23.6±18.9

L: Left, R: Right, n: Number, SD: Standard deviation, VATS: Video-assisted thoracoscopic surgery, DM: Diabetes mellitus

was detected in terms of variables between patients who developed mortality and were discharged (Table 3). In patients developing mortality, a more exudative fluid at a statistically significant level was observed, whereas more transudative fluid was detected in the patients who were discharged (p=0.08).

Pathological examination revealed that all 5 patients with malignant cells in PE had a previous history of primary cancer (2 had gastric cancer, 1 had breast cancer, 1 had acute myeloblastic leukemia, and 1 had acute lymphoblastic leukemia). Malignant cells were detected in the pleural fluid in 10% of patients in primary malignancy cases (n=50) and no malignant cell was detected in the pleural fluid of patients without a diagnosis of malignancy (n=53), and the difference was statistically significant (p=0.02).

The total LOS was determined to be significantly higher in patients undergoing a second surgical procedure compared to patients not requiring it (31.7±12.7 days vs. 20.1±15.6 days, p=0.009).

DISCUSSION

In the United States, 1.4 million people have been reported to develop PE annually. The most common causes of PE are congestive heart failure, pneumonia, and cancers, whereas pulmonary embolism, viral diseases, coronary bypass surgery, cirrhosis, intra-abdominal diseases, and uremia diseases were reported to follow as less frequent (10-12). Concurrently, conditions, such as the increased number of patients with chronic diseases due to the prolongation of life expectancy and an increased incidence of malignancies, suggest that patients with PE will increase in the future. Therefore, determination for the best procedure for these patients is crucial.

In the current study, all patients undergoing drainage due to PE were found to have a comorbidity, and 3 or more comorbidities were observed simultaneously in most of them (51%). In studies, heart failure is the most common cause of PE (8-10), followed by breast, lung, and pleural metastatic cancer (10-12).

A study evaluated 2,040 patients with malignant PE and revealed that malignancies originating from the lung (38%), breast (17%), lymphoma (12%), genitourinary system (9%), and gastrointestinal system (7%) have been reported (13). Similar results were obtained in the current study. In heart failure, renal diseases, hypoalbuminemia, and some pulmonary diseases, pleural fluid slowly begins to regress after the disease is controlled by medical treatment (14).

Table 2. Comparison of variables according to the type of pleural effusion

Variables	Transudative (n=54)	Exudative (49)	p
Age, year ± SD	63.2±17.0	61.6±16.5	0.574
Sex, n (%)			
Male	33 (61.1%)	25 (51.0%)	0.302
Female	21 (38.9%)	24 (49.0%)	
Number of comorbidities, n (%)			
1	18 (33.3%)	15 (30.6%)	
2	7 (13.0%)	10 (20.4%)	0.596
3 or more	29 (53.7%)	24 (49.0%)	
Malignancy presence, n (%)	21 (38.9%)	29 (59.2%)	**0.04**
DM, n (%)	16 (29.6%)	14 (28.6%)	0.906
Cardiac disease group, n (%)	31 (57.4%)	29 (59.2%)	0.855
Renal disease group, n (%)	15 (27.8%)	12 (24.5%)	0.705
Pulmonary disease group, n (%)	17 (31.5%)	5 (10.2%)	**0.009**
Pleural effusion side, n (%)			
L	20 (37.0%)	12 (24.5%)	0.06
R	32 (59.3%)	31 (63.3%)	
Bilateral	2 (3.7%)	**6 (12.2%)**	
Malignancy detection in pleural fluid, n (%)	1 (1.9%)	4 (8.2%)	0.189
Duration of drainage, day ± SD	8.5±9.3	9.2±7.4	0.763
Need for a second surgical procedure at hospitalization, n (%)	19 (35.2%)	12 (24.5%)	0.237
Length of hospitalization, day ± SD	23.7±16.8	23.5±21.2	0.451

L: Left, R: Right, n: Number, SD: Standard deviation, DM: Diabetes mellitus. P values marked with Bold show statistical significance. The p-value written in italics shows that there is a statistically close relationship to significance

However, in PEs accumulating due to any malignancy, recurrent fluid accumulation in the pleural cavity may be observed after surgical drainage. Pleural drainage in these patients provides short-term symptomatic improvement (14). Therefore, the decision for pleural fluid drainage should be taken with a multidisciplinary approach, and treatment strategies should be determined before and after drainage.

Frequently, patients had drainage using a thin-diameter pleural drainage catheter, but complications developed in one out of every ten patients undergoing drainage. In addition, an additional pleural intervention was required in one of every three patients whose pleural catheter was removed after the drainage was thought to be medically and surgically completed. In the literature, 5%-12% of patients undergoing pleural fluid drainage have been reported to develop complications (14-17). In the current study, post-procedural complications developed in 11 (10.7%) patients. These results were consistent with the literature.

Therefore, close follow-up of patients undergoing pleural drainage in terms of possible complications (often pneumothorax) is important. In addition, frequent recurrences in patients with a pleural catheter removal due to drainage completion and lung expansion suggest the need for aggressive treatment for the primary condition. It should be kept in mind that pleural fluid accumulates again as the primary disease is not controlled medically.

Table 3. Comparison of mortality and discharged patients

Variables	Discharge (n=89)	Ex (n=14)	p
Age, year ± SD	62.9±16.5	59.6±18.4	0.551
Sex, n (%) **Male** **Female**	 48 (53.9%) 41 (46.1%)	 10 (71.4%) 4 (28.6%)	0.259
Anticoagulant drug use, n (%)	10 (11.2%)	2 (14.3%)	0.666
Number of comorbidities, n (%) **1** **2** **3 or more**	 30 (33.7%) 15 (16.9%) 44 (49.4%)	 3 (21.4%) 2 (14.3%) 9 (64.3%)	0.293
Malignancy presence, n (%)	41 (46.1%)	9 (64.3%)	0.205
DM, n (%)	26 (29.2%)	4 (28.6%)	1.000
Cardiac disease group, n (%)	51 (57.3%)	9 (64.3%)	0.622
Renal disease group, n (%)	22 (24.7%)	5 (35.7%)	0.385
Pulmonary disease group, n (%)	19 (21.3%)	3 (21.4%)	1.000
Pleural effusion side, n (%) **L** **R** **Bilateral**	 30 (33.7%) 52 (58.4%) 7 (7.9%)	 2 (14.3%) 11 (78.6%) 1 (7.1%)	0.263
The type of surgical intervention performed first, n (%) **Pleural catheter** **Tube thoracostomy** **VATS**	 84 (94.4%) 4 (4.5%) 1 (1.1%)	 13 (92.9%) 1 (7.1%) 0 (0.0%)	0.961
Surgery-related complication, n (%)	10 (11.2%)	1 (7.1%)	1.000
Type of PE, n (%) **Transudate** **Exudate**	 50 (56.2%) 39 (43.8%)	 4 (28.6%) 10 (71.4%)	0.08
Malignancy detection in pleural fluid, n (%)	5 (5.6%)	0 (0.0%)	1.000
Duration of drainage, day ± SD	8.9±8.8	8.7±5.5	0.636
Need for a second surgical procedure at hospitalization, n (%)	27 (30.3%)	4 (28.6%)	1.000
Length of hospitalization, day ± SD	24.8±19.8	16.2±8.8	0.160

L: Left, R: Right, n: Number, SD: Standard deviation, VATS: Video-assisted thoracoscopic surgery, The *p*-value written in italics shows that there is a statistically close relationship to significance

The number of comorbidities was not found to be significant in terms of the discrepancy between the transudative and exudative fluid, whereas the presence of fluid was observed to differ according to the additional comorbidity. Exudative fluid was frequently observed in patients diagnosed with malignancy, whereas transudative fluid was significantly higher in patients with pulmonary disease. Malignancies are among the most common causes of exudative PE in the studies performed (11,18).

Exudative fluid has been often expected in patients with pulmonary diseases, contrarily, in the current study, transudate fluid was more common in those patients due to the concurrent presence of additional comorbidities, especially cardiac diseases, in those with pulmonary disease.

Considering that the causes of mortality in the United States of America have been examined with age-standardized rates, the mortality rate of patients with pleural fluid has been generally reported as 0.0003%. Data on mortality due to PEs are generally associated with malignant pleural fluids, which is identified with high mortality (19). Studies reported that patients with malignant PE have a high mortality rate. Moreover, mortality was reported in patients with benign etiology, congestive heart failure, and renal failure, which are among the causes of PE. Studies in the literature regarding mortality in non-malignant PEs are limited. In addition, studies reported that bilateral PE is linked with high mortality (19).

In our study, the rate of mortality was not changed by any of the factors. However, a high mortality rate was detected at a level close to statistical significance in patients with both malignancy and exudative fluid, which is also compatible with the literature. In addition, it should not be forgotten that this mortality rate belongs only to hospitalized patients. Thus, results may change during the follow-up examination.

Performing a cytological examination of the pleural fluid in every patient who is hospitalized with PE is still controversial. In the present study, every patient who was found to have malignant pleural fluid on cytological examination had a history of the primary malignancy. No malignancy was detected in the pleural fluid of patients without primary malignancy. Studies in the literature reported that cytological studies were performed in patients who were diagnosed with primary malignancy or who were thought to have malignancy with a high probability. This situation in the current study is compatible with cytological studies in the literature (20). Thus, cytological analysis is thought to be ineffective in patients without a primary malignancy or a pre-diagnosis in this context.

This retrospective study observed a long LOS of patients hospitalized and undergoing pleural drainage due to PE. The average LOS of all patients was 23.6 days. Among these patients, this period was even longer in patients undergoing surgical drainage for the second time, which was 31.7 days on average. Studies evaluating patients who did not undergo pleural drainage reported a shorter LOS. The average LOS was reported to be 4.1±6.2 days (21) in a study in which patients who are hospitalized for upper gastrointestinal bleeding were evaluated. Another study examining the community-acquired pneumonia cases detected an average LOS of 11.1 days (22).

Study Limitations

One of the limitations of our study is its retrospective nature. Other limitations are the number of cases and compromising only drainage applied to patients.

CONCLUSION

Patients who are hospitalized with PE-caused drainage indicated at least one systemic disease. The most common is cardiac disease. The number of post-drainage complications is moderate; however, major complications are not frequent. Factors affecting the mortality were often due to the primary systemic disease of the patient, whereas the type of PE being exudative may be predictive in terms of mortality. Malignant cells are likely seen in the pleural fluid in the developing PE in patients with malignancy, thus patients without known previous malignancy and those with comorbidities that may cause transudative PE, such as heart failure, renal insufficiency, and systemic infections, cytological examination of the pleural fluid may not be requested unless there is strong suspicion. The rate of second pleural surgery is high in PE, thus the LOS of patients is prolonged.

ETHICS

Ethics Committee Approval: The study was obtained from the Ethics Committee of the University of Health Sciences Turkey, Bakırkoy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2021/96).

Informed Consent: Informed consent for the patient's information was obtained from the patient(s) or a legally authorized representative before hospitalization.

Authorship Contributions

Surgical and Medical Practices: S.Ö., F.K., N.Ç., Concept: S.Ö., A.K., Design: S.Ö., N.Ç., M.Ö.U., Data Collection or Processing: S.Ö., F.K., N.Ç., Analysis or Interpretation: S.Ö., F.K., N.Ç., M.Ö.U., Literature Search: S.Ö., N.Ç., Writing: S.Ö., F.K., N.Ç., M.Ö.U., A.K.

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. Kaplan G, Yakut İH, Cinel G. Çocukluk Çağı Plevral Efüzyon Nedenleri, Klinik Bulguları ve Yönetimi; Retrospektif Bir Analiz. Türkiye Çocuk Hast Derg 2021;1:1-5.
2. Çıtak N, Omaygenç DÖ. Plevral Efüzyonda Cerrahi Tedavi Yöntemleri: Tekrarlayan Torasentez, Tüp Torakostomi, Kimyasal Plörodezis, Kalıcı Plevral Kateter, Plevroperitoneal Şant ve Plevrektomi/Dekortikasyon. Güncel Göğüs Hastalıkları Serisi 2015;3:362-79.
3. Metintaş S. Plevral sıvıların epidemiyolojisi. İç: Gözü O, Köktürk O, ed. Plevra hastalıkları. Ankara: Toraks Kitapları-Toraks Derneği Yayınları; 2003:16-23.
4. Hooper C, Lee YG, Maskell N. Erişkinlerdeki tek tarafli plevral efüzyonlarin araştirilmasi: britanya toraks derneği plevral hastaliklar kılavuzu 2010:1-20.
5. Miserocchi G. Physiology and pathophysiology of pleural fluid turnover. Eur Respir J 1997;10:219-25.
6. Light RW. Clinical practice. Pleural effusion. N Engl J Med 2002;346:1971-7.
7. Esendağlı D, Maden E. Sistemik hastalıklarına bağlı plevral efüzyon. Güncel Göğüs Hastalıkları Serisi 2015;3:402-8.
8. Maskell NA, Butland RJ; Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the investigation of a unilateral pleural effusion in adults. Thorax 2003;58:ii8-17.
9. McGrath EE, Anderson PB. Diagnosis of pleural effusion: a systematic approach. Am J Crit Care 2011;20:119-28.
10. Light RW. Diagnostic principles in pleural disease. Eur Respir J 1997;10:476-81.
11. Marel M. Epidemiology of pleural effusions. Eur Respir Mon 2002;22:146-56.
12. Light RW. Diagnostic approach in a patient with pleural effusion. Eur Respir Mon 2002;22:131-6.
13. Antunes G, Neville E, Duffy J, Ali N; Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the management of malignant pleural effusions. Thorax 2003;58:ii29-38.
14. Koyuncu N. İbrahim A. Pleuracan Drainage due to Pleural Effusion in the Emergency Department Haydarpasa Numune Med J 2019;59:60-3.
15. Kohan JM, Poe RH, Israel RH, Kennedy JD, Benazzi RB, Kallay MC, et al. Value of chest ultrasonography versus decubitus roentgenography for thoracentesis. Am Rev Respir Dis 1986;133:1124-6.
16. Collins TR, Sahn SA. Thoracocentesis. Clinical value, complications, technical problems, and patient experience. Chest 1987;91:817-22.
17. Bartter T, Mayo PD, Pratter MR, Santarelli RJ, Leeds WM, Akers SM. Lower risk and higher yield for thoracentesis when performed by experienced operators. Chest 1993;103:1873-6.
18. Maartens G, Bateman ED. Tuberculous pleural effusions: increased culture yield with bedside inoculation of pleural fluid and poor diagnostic value of adenosine deaminase. Thorax 1991;46:96-9.
19. DeBiasi EM, Pisani MA, Murphy TE, Araujo K, Kookoolis A, Argento AC, et al. Mortality among patients with pleural effusion undergoing thoracentesis. Eur Respir J 2015;46:495-502.
20. Hsu C. Cytologic detection of malignancy in pleural effusion: a review of 5,255 samples from 3,811 patients. Diagn Cytopathol 1987;3:8-12.
21. Sarı O, Tanoğlu A, İnal V, Türkoğlu Hİ, Öztürk B, Sağlam K. GATA Acil Dahiliye Kliniğinde üst gastrointestinal sistem kanaması nedeniyle 1998-2005 yılları arasında takip edilen hastaların sosyodemografik özelliklerinin incelenmesi. Gülhane Tıp Dergisi 2007;49;4:226-31.
22. Pişkin N, Aydemir H, Oztoprak N, Akduman D, Celebi G, Seremet Keskin A. Toplum kökenli pnömoni olgularinda hastanede yatiş süresi ve mortaliteyi etkileyen faktörler [Factors effecting the duration of hospitalization and mortality in patients with community-acquired pneumonia]. Mikrobiyol Bul 2009;43:597-606.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:312-319
DOI: 10.4274/BMJ.galenos.2021.03411

Research

Management Strategies for Acute Cholecystitis: Is the Timing of Surgery Important?

Akut Kolesistit için Tedavi Stratejileri: Cerrahi Zamanlamasının Bir Önemi Var Mıdır?

Özgür Ekinci[1], Tunç Eren[1], Aman Gapbarov[1], Damla Beyazadam[1], Nurgül Bulut[2], Metin Leblebici[1], Orhan Alimoğlu[1]

[1]Istanbul Medeniyet University Göztepe City Hospital, Department of General Surgery, Istanbul, Turkey
[2]Istanbul Medeniyet University, Department of Biostatistics and Medical Informatics, Istanbul, Turkey

ABSTRACT

Objective: The timing of cholecystectomy is still controversial in acute cholecystitis (AC). This study aimed to evaluate the outcomes of early cholecystectomy (EC), delayed cholecystectomy (DC), and non-operative management (NOM) for AC.

Methods: The patients with AC, who were treated in a one-year-period, were divided into EC, DC, and NOM subgroups. Parameters, including demographics, laboratory results, imaging findings, body mass index (BMI), American Society of Anesthesiologists (ASA) score, the timing of surgery, operative time, gallstone size, postoperative complications, and postoperative length of hospital stay were analyzed.

Results: The study group of 125 patients comprised of 71 patients (56.8%) in the EC, 29 (23.2%) in the DC, and 25 patients (20%) in the NOM group. Patients in the NOM group were relatively older ($p<0.05$). BMI values and physical examination findings were similar among the subgroups ($p>0.05$). The incidence of ASA score of 3 and the mean levels of bilirubin, aspartate aminotransferase, and alanine aminotransferase was higher, whereas the mean hemoglobin value was lower in the NOM group ($p<0.05$). Gallstones smaller than 1 cm were more common in the DC group ($p<0.05$). The mean operative times, conversion rates, and postoperative complications were similar between the EC and DC groups ($p>0.05$). The length of hospital stay was shorter in the DC group ($p<0.05$).

Conclusion: The surgical treatment of hospitalized patients with AC can be performed anytime within the first week of their admissions unless the clinical and laboratory findings render the patient unfit for surgery.

Keywords: Gallbladder, acute cholecystitis, cholecystectomy, general surgery

ÖZ

Amaç: Akut kolesistit (AK) olgularında kolesistektominin zamanlaması halen tartışmalıdır. Bu çalışmanın amacı, AK için erken kolesistektomi (EK), geç kolesistektomi (GK) ve non-operatif tedavi (NOT) sonuçlarının karşılaştırılmasıdır.

Gereç ve Yöntem: Bir yıllık süreçte AK tanısıyla tedavi edilen hastalar EK, GK ve NOT alt gruplarına ayırıldı. Demografik veriler, laboratuvar sonuçları, görüntüleme bulguları, vücut kitle indeksi (VKİ), Amerikan Anestiyoloji Derneği (ASA) skoru, cerrahi zamanlaması, ameliyat süresi, safra taşı boyutu, postoperatif komplikasyonlar ve postoperatif hastanede yatış süresini içeren parametreler analiz edildi.

Bulgular: Çalışmaya dahil olan 125 hastanın; 71'i (%56,8) EK grubunda, 29'u (%23,2) GK grubunda ve 25'i (%20) NOT grubundaydı. Hastalardan NOT grubunu oluşturanlar, göreceli olarak daha yaşlı idi ($p<0,05$). Çalışma alt grupları arasında VKİ değerleri ve fizik muayene bulguları benzerdi ($p>0,05$). Alt gruplardan NOT grubunda; ASA 3 skoru sıklığı, ortalama bilirubin değerleri ile aspartat aminotransferaz ve alanin aminotransferaz değerleri daha yüksek iken ortalama hemoglobin değeri daha düşüktü ($p<0,05$). Boyutları 1 cm'den küçük safra taşları GK grubunda daha sık olarak gözlendi ($p<0,05$). Ortalama ameliyat süresi, açık ameliyata geçiş oranları ve postoperatif komplikasyon oranları EK ve GK grupları arasında benzer saptandı ($p>0,05$). Hastanede yatış süresinin GK grubunda daha kısa olduğu gözlendi ($p<0,05$).

Address for Correspondence: Tunç Eren, Istanbul Medeniyet University Göztepe City Hospital, Department of General Surgery, Istanbul, Turkey
Phone: +90 532 244 74 94 E-mail: drtunceren@gmail.com ORCID ID: orcid.org/0000-0001-7651-4321

Cite as: Ekinci Ö, Eren T, Gapbarov A, Beyazadam D, Bulut N, Leblebici M, Alimoğlu O. Management Strategies for Acute Cholecystitis: Is the Timing of Surgery Important? Med J Bakirkoy 2021;17:312-319

Received: 27.04.2021
Accepted: 19.11.2021

Sonuç: Klinik ve laboratuvar bulguları hastanın ameliyat için uygun olmadığını göstermediği sürece, akut kolesistit olgularının cerrahi tedavisi, hastaneye yatışın ilk haftası içerisinde herhangi bir zamanda gerçekleştirilebilir.

Anahtar Kelimeler: Safra kesesi, akut kolesistit, kolesistektomi, genel cerrahi

INTRODUCTION

Laparoscopic cholecystectomy (LC) was first performed by Mühe in 1985 and was accepted as a safe and effective treatment method for symptomatic gallstone disease by the National Institutes of Health in 1992 (1,2). Approximately, 80% of patients harboring gallstones are asymptomatic (3). When symptomatic gallstones obstruct the cystic duct, the subsequent distension of the gallbladder may be complicated with inflammation, infection, and ischemia that lead to acute cholecystitis (AC) (4). Annually, 1-2% of patients with gallstones present with biliary colic, jaundice, and biliary pancreatitis, whereas AC develops in 10% of cases (5,6).

Epigastric and/or right upper quadrant pain, as well as Murphy's sign, are the common physical examination findings of AC (3). White blood cell (WBC) count and C-reactive protein (CRP) levels are usually elevated (4). Imaging studies frequently reveal a thickened gallbladder wall and pericholecystic fluid in cases with AC (7).

According to the latest updated Tokyo guidelines in 2018, the diagnostic criteria for AC are based on the local and systemic signs of inflammation in addition to the imaging findings (1). Pain, tenderness, and/or a palpable mass in the right upper quadrant and Murphy's sign are the local signs, whereas fever, elevated WBC count, and a raised CRP level are the systemic signs of inflammation. Characteristic imaging findings for AC include the measurement of the gallbladder wall thickness of ≥5 mm, the presence of pericholecystic fluid, and the detection of abdominal tenderness by the pressure of the probe at ultrasonographic evaluation (sonographic Murphy's sign) (8,9).

There's no doubt that LC is the treatment of choice for AC; however, the timing for the operation is still controversial (10). According to the 2018 Tokyo guidelines, early cholecystectomy (EC) that is to be performed within the first week after the onset of AC symptoms is recommended (11). Thus, this study aimed to evaluate the treatment outcomes of patients with AC, either having undergone (EC) or delayed cholecystectomy (DC), or having been managed non-operatively (NOM).

METHODS

The data of patients treated with the diagnosis of AC in the Department of General Surgery between July 2018 and July 2019 was prospectively recorded and retrospectively analyzed. This study was approved by the Institutional Review Ethics Committee of Istanbul Medeniyet University Göztepe City Hospital (IRB: 2019/0327). Signed informed consent forms were obtained from all patients. All procedures were performed following the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

In all included patients, the diagnosis of AC was made based on their findings following the diagnostic criteria of the 2018 Tokyo guidelines. All patients were offered surgery following the diagnostic evaluations, and were divided into three subgroups: 1) EC group included patients who underwent cholecystectomy at any time during their index admission, 2) DC group included patients who underwent cholecystectomy after 4-6 weeks following their initial medical treatment as this subgroup comprised of patients who refused the proposed early surgical intervention during their first hospitalization period, 3) NOM group included patients who did not undergo cholecystectomy following their initial medical treatment since they were unfit for surgery or refused the surgical treatment option.

Patients who presented with biliary colic, diagnosed with an acute abdomen, younger than 18 or older than 90 years old, and were initially treated with percutaneous cholecystostomy were excluded from the study. Parameters, including demographics, laboratory results, imaging findings, body mass index (BMI), American Society of Anesthesiologists (ASA) score, the timing of surgery, operative time, gallstone size, postoperative complications, and postoperative length of hospital stay, were recorded and compared among the groups.

Statistical Analysis

Statistical analyses were performed using the International Business Machines® Statistical Package for the Social Sciences® version 22.0 Software (IBM Industries, New York, USA). In addition to the descriptive statistical methods (mean, standard deviation, median, minimum, maximum, and ratio), the Mann-Whitney U test was used to compare numerical quantities of parameters with abnormal distribution between the two groups. Differences among more than two groups with normal distribution were analyzed with the analysis of variance, whereas the Kruskal-Wallis test was used for maldistribution among the groups.

Significance in multiple comparisons was evaluated via post-hoc tests, including Tukey and Bonferroni corrections, whereas Pearson's Chi-squared test was used for categorical data analysis. Differences were considered statistically significant with p-values of <0.05.

RESULTS

The study group of 125 patients with AC comprised 71 (56.8%) patients in the EC, 29 (23.2%) in the DC, and 25 (20%) in the NOM group. The EC group consisted of 37 (52.1%) males and 34 (47.9%) females with a mean age of 51.5±14.0 (range: 20-86) years, whereas the DC group consisted of 15 (51.7%) males and 14 (48.3%) females with a mean age of 55.9±11.3 (range: 25-72) years and the NOM group consisted of 16 (64.0%) males and 9 (36.0%) females with a mean age of 76.6±11.9 (range: 45-94) years. Patients in the NOM group were relatively older than the other subgroups (p=0.001). No statistically significant difference was found among the subgroups concerning gender (p=0.559) (Table 1).

The mean BMI value of the EC group was 28.9±4.6 (range: 19.6-47.2), whereas the DC group was 28.5±4.0 (range: 22.6-37.9) and the NOM group was 26.8±4.2 (range: 16.2-33.4), which reveal no significant difference among the subgroups (p=0.178). The ASA score evaluation revealed that patients with the ASA scores of 1 and 2 were more common in the EC group, whereas the incidence of ASA score of 3 was significantly higher in the NOM group (p=0.039) (Table 1).

Regarding the laboratory results, the mean levels of total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were significantly higher in the DC and NOM groups compared to the EC group (p=0.033, p=0.001, and p=0.036, respectively). The mean direct bilirubin levels were significantly higher in the EC than the NOM group and the mean lactate dehydrogenase levels were significantly higher in the DC group (p=0.020 and p=0.031, respectively). Contrarily, the mean hemoglobin value of the NOM group was significantly lower than the other subgroups (p=0.008) (Table 2).

According to the physical examination findings, sole right upper quadrant pain without the presence of Murphy's sign was found in 23 (32.4%) patients, whereas 48 (67.6%) patients presented with accompanying Murphy's sign in the EC group. Right upper quadrant pain was solely present in 8 (27.6%) patients in the DC group and 9 (36%) in the NOM group, whereas accompanying Murphy's sign was found in 21 (72.4%) patients in the DC group and 16 (64%) in the NOM group. No statistical differences were detected among the three subgroups according to the physical examination findings (p=0.799) (Table 3).

The DC group had 16 (55.2%) patients who harbored gallstones that were <1 cm, whereas gallstones with a size of 1 cm or larger were detected in 48 (67.6%) patients in the EC group and 14 (56.0%) patients in the NOM group. Gallstones smaller than 1 cm were significantly more common in the DC group compared to the other subgroups (p=0.001) (Table 3).

The mean duration between the onset of symptoms and the time of cholecystectomy was calculated to be 130.0±86.9 (range: 24-480) h in the EC group. The mean operative time was 68.3±38.4 (range: 10-180) min in the EC group and 72.3±36.2 (range: 24-480) min in the DC group, without statistically significant difference (p=0.495) (Table 3).

All cholecystectomies were started laparoscopically. In the EC group, LC was completed in 69 (97.2%) patients, whereas conversion to open surgery occurred in 2 (2.8%) patients. Contrarily, LC was completed in 26 (89.7%) and

Table 1. The distribution of demographic parameters among patient groups

Patient groups			EC	DC	NOM	p
n (%)			71 (56.8%)	29 (23.2%)	25 (20%)	
Gender	Male	n (%)	37 (52.1%)	15 (51.7%)	16 (64.0%)	0.559[a]
	Female		34 (47.9%)	14 (48.3%)	9 (36.0%)	
Age (years)		Mean±SD (range)	51.5±14.0 (20-86)	55.9±11.3 (25-72)	76.6±11.9 (45-94)	0.001[b]
Body mass index (kg/m^2)		Mean±SD (range)	28.9±4.6 (19.6-47.2)	28.5±4.0 (22.6-37.9)	26.8±4.2 (16.2-33.4)	0.126[b]
ASA score	I	n (%)	16 (22.5%)	6 (20.7 %)	2 (8.0%)	0.039[a]
	II		50 (70.4%)	21 (72.4%)	16 (64.0%)	
	III		5 (7.0%)	2 (6.9%)	7 (28.0%)	

[a]Pearson's chi-squared test, [b]analysis of variance, SD: Standard deviation, n: Number of patients, EC: Early cholecystectomy, DC: Delayed cholecystectomy, NOM: Non-operative management, ASA: American Society of Anesthesiologists

Table 2. The distribution of laboratory parameters among patient groups

Laboratory parameter	Study group	Mean	±SD	Median	Min	Max	p	Post hoc (groups)
White blood cell count (10^3/μL)	EC	13.0	3.7	12.9	5.9	23.2	0.087[a]	N/A
	DC	14.0	4.8	13.4	5.4	29.5		
	NOM	11.6	5.9	10.4	4.8	32.6		
Hemoglobin (g/dL)	EC	13.7	1.6	13.7	10.2	17.1	**0.008**[a]	NOM<EC, DC
	DC	14.1	1.6	14.5	10.2	16.5		
	NOM	12.7	1.8	1.5	9.6	16.9		
Total bilirubin (mg/dL)	EC	1.0	0.6	0.8	0.1	2.8	**0.033**[b]	EC<DC, NOM
	DC	1.4	1.2	1.0	0.3	5.1		
	NOM	1.5	1.2	1.2	0.6	4.4		
Direct bilirubin (mg/dL)	EC	0.4	0.3	0.3	0.1	1.6	**0.020**[b]	EC<NOM
	DC	0.6	0.6	0.3	0.1	2.5		
	NOM	0.9	0.8	0.6	0.1	3.2		
Indirect bilirubin (mg/dL)	EC	0.6	0.4	0.6	0.0	2.0	0.250[b]	N/A
	DC	0.8	0.8	0.7	0.2	4.3		
	NOM	0.6	0.4	0.5	0.1	1.3		
C-reactive protein (mg/dL)	EC	6.3	7.4	4.0	0.1	34.0	0.571[b]	N/A
	DC	5.5	9.4	0.9	0.1	32.3		
	NOM	6.7	7.9	3.8	0.1	31.1		
Aspartate aminotransferase (IU/L)	EC	30.3	42.3	20.0	10.0	323.0	**0.001**[b]	EC<DC, NOM
	DC	92.9	97.3	46.5	8.0	376.0		
	NOM	103.0	109.5	35.0	8.8	417.0		
Alanine aminotransferase (IU/L)	EC	34.7	41.7	20.0	10.0	235.0	**0.036**[b]	EC<DC, NOM
	DC	93.5	114.9	35.0	9.0	384.0		
	NOM	86.9	93.3	43.0	8.0	359.0		
Gamma-glutamyl transferase (IU/L)	EC	65.0	90.7	35.0	10.0	562.0	0.092[b]	N/A
	DC	221.9	309.8	42.0	14.0	1093.0		
	NOM	237.0	288.1	77.5	12.0	961.0		
Alkaline phosphatase (IU/L)	EC	96.7	51.9	86.0	39.0	360.0	0.262[b]	N/A
	DC	112.1	67.7	85.0	52.0	317.0		
	NOM	149.5	122.3	93.5	62.0	570.0		
Lactate dehydrogenase (IU/L)	EC	226.4	76.9	212.0	0.0	591.0	**0.031**[b]	EC<DC
	DC	295.7	121.0	270.5	149.0	589.0		
	NOM	261.8	92.2	231.0	168.0	523.0		
Amylase (IU/L)	EC	53.0	27.1	47.0	12.0	138.0	0.182[b]	N/A
	DC	82.1	81.0	52.5	24.0	377.0		
	NOM	96.2	113.0	65.5	19.0	544.0		

[a]analysis of variance (post-hoc: Tukey), [b]Kruskal-Wallis (post-hoc: Bonferroni), SD: Standard deviation, Min: Minimum, Max: Maximum, N/A: Not applicable
EC: Early cholecystectomy, DC: Delayed cholecystectomy, NOM: Non-operative management

conversion took place in 3 (10.3%) patients in the DC group. The conversion rates were found to be similar between the two subgroups (p=0.117) (Table 3).

In the early postoperative period, 66 (93.0%) patients in the EC and 27 (93.1%) in the DC group were observed to be free of complications as they were discharged eventless. However, the EC group had 5 (7.0%) patients who developed postoperative complications including atelectasis, pulmonary embolism, hemorrhage, intraabdominal fluid collection, and cystic stump leakage. Contrarily, the DC group had 2 (6.9%) patients who developed postoperative complications, which were intraabdominal fluid collection and hyperbilirubinemia. No significant difference was detected between the EC and DC groups regarding postoperative complications (p=0.608) (Table 3).

The mean duration of postoperative hospital stay was calculated as 2.3±2.4 (range: 1-15) days in the EC group and 1.7±2.0 (range: 1-9) days in the DC group. The length of hospital stay was shorter in the DC group (p=0.001) (Table 3).

DISCUSSION

Females are more likely to develop gallstones with an approximately threefold prevalence compared to males, and 90-95% of AC cases occur due to complicated gallstone disease (12). To date, controversy still exists regarding the best management method and timing of surgery for AC (10).

A meta-analysis published by Gallagher et al. (13) indicated that the mean age of patients in the EC and DC groups were 55.0 and 56.5, respectively. Our study revealed that the mean ages of patients in the EC and DC groups were 51.5 and 55.9, respectively, whereas in the NOM group was 76.6 years. The mean age of patients in the NOM group was significantly higher compared with the other groups (p<0.05). The elder patients who also have comorbidities would be unfit for surgery, thus the rates of NOM, which included broad-spectrum antibiotherapy and percutaneous cholecystostomy, were higher. However, a fewer number of younger patients were in the NOM group since these patients refused surgical treatment.

Table 3. The distribution of clinical parameters and surgical outcomes among patient groups

Patient groups			EC	DC	NOM	p
n (%)			71 (56.8%)	29 (23.2%)	25 (20%)	
Physical examination	Right upper quadrant tenderness only	n (%)	23 (32.4%)	8 (27.6%)	9 (36.0%)	0.799[a]
	Murphy's sign		48 (67.6%)	21 (72.4%)	16 (64.0)	
Gallstone/ sludge	Sludge	n (%)	2 (2.8%)	3 (10.3%)	6 (24.0%)	**0.001[a]**
	Gallstone <1 cm		21 (29.6%)	16 (55.2%)	5 (20.0%)	
	Gallstone ≥1 cm		48 (67.6%)	10 (34.5%)	14 (56.0%)	
Time since onset of symptoms (hours)		Mean ± SD (range)	130.0±86.9 (24-480)	-	-	N/A
Type of surgery	Laparoscopic cholecystectomy	n (%)	69 (97.2%)	26 (89.7%)	-	0.117[a]
	Conversion to open surgery		2 (2.8%)	3 (10.3%)	-	
Operative time (minutes)		Mean ± SD (range)	68.3±38.4 (10-180)	72.3±36.2 (24-480)	-	0.495[c]
Complication	None	n (%)	66 (93.0%)	27 (93.1%)		0.608[a]
	Atelectasis		1 (1.4%)	-	-	
	Pulmonary embolism		1 (1.4%)	-	-	
	Hemorrhage/laparotomy		1 (1.4%)	-	-	
	Intraabdominal fluid collection		1 (1.4%)	1 (3.5%)	-	
	Cystic stump leakage		1 (1.4%)	-	-	
	Hyperbilirubinemia		-	1 (3.5 %)	-	
Postoperative hospital stay (days)		Mean±SD (range)	2.3±2.3 (1-15)	1.7±1.9 (1-9)	-	**0.001[c]**

[a]Pearson's chi-squared test, [b]analysis of variance, [c]Mann-Whitney U test, n: Number of patients, SD: Standard deviation, N/A: Not applicable, EC: Early cholecystectomy, DC: Delayed cholecystectomy, NOM: Non-operative management

The current 2018 Tokyo Guidelines suggest that diagnostic criteria for AC include Murphy's sign and right upper quadrant pain (1). Murphy's sign was the most common physical examination finding in our EC and DC groups; however, no significant difference was detected among the subgroups regarding physical examination findings ($p>0.05$).

Cystic duct obstruction by gallstones is the main reason for the development of AC (4). Our study demonstrates that subsentimetric gallstones were significantly higher in the DC group, whereas gallstones of >1 cm were mostly detected in the EC and NOM groups ($p<0.05$). Subsentimetric gallstones that cause AC have a higher probability to cause abnormalities in laboratory findings; hence, leading to time-consuming additional investigations to evaluate the biliary tract, which is considered the main reason for preferring management with medical treatment and DC following >4-6 weeks in cases of gallstones of <1 cm. However, the relation between early or late cholecystectomies and gallstone size is yet controversial.

Patients who present with AC might also have accompanying laboratory findings, such as high levels of bilirubin and transaminases (12). The extrahepatic biliary tract must be evaluated with magnetic resonance cholangiopancreatography in the absence of spontaneous recovery in the laboratory findings because of the increased risks of postoperative complications, such as jaundice and cystic stump leakage. Then, cholangiographic evaluation and gallstone extraction should be performed via endoscopic retrograde cholangiopancreatography (ERCP) if indicated (14). Our findings reveal that laboratory parameters, including total bilirubin, direct bilirubin, AST, and ALT, were observed to be lower in the EC group compared to the other two groups ($p<0.05$). We agree that should the bilirubin and liver enzymes are elevated, EC ought to be avoided and LC should be delayed until the values reach normal limits.

One of the risk factors that are associated with prolonged surgery and conversion to open surgery is high BMI (1,15). Our study revealed that the mean BMI value was 28.06 kg/m^2, without statistically significant difference compared among the study subgroups ($p>0.05$).

Opinions are presented that elderly patients with ASA scores of ≥2 will have cardiopulmonary side effects of pneumoperitoneum; however, the postoperative results of LC in the elderly patients have been satisfactory (16). Our study found that patients with an ASA score of 3 were significantly higher in the NOM group than in the other subgroups ($p<0.05$).

Studies that question the paradigm regarding the concept of "the first 72-96 hours" requirement for EC that even took place in reference textbooks report that this period can be extended up to 168 h (11,12). Our study revealed that patients in the EC group were operated on an average of 5.4 days (130.0±86.9 h) following the onset of symptoms. Contrary to other studies, our patients underwent cholecystectomy within the first week after their hospitalization, regardless of the duration from the onset of complaints, which is considered a bold surgical approach. However, the comparative statistical analysis between the EC group in which the patients were operated on in the first week regardless of the onset of their symptoms and the DC group in which the operations were performed after 4-6 weeks demonstrated no significant difference in terms of complication rates between the two subgroups ($p<0.05$).

Additionally, the mean operative time was calculated as 70.0±39.9 min in the EC group and 72.3±36.2 min in the DC group, without statistically significant difference ($p<0.05$).

Gurusamy et al. (17) compared the groups of EC and DC and reported similar rates of biliary tract injury and conversion. Our study revealed no biliary tract injuries in patients who underwent cholecystectomy, and no statistically significant difference was found between the EC and DC groups regarding the conversion rates ($p>0.05$).

One of the most common complications following cholecystectomy includes bile duct leakage due to the presence of a Luschka duct. Peritonitis, bleeding, surgical site infection, and intraabdominal collection are other complications that might develop after cholecystectomy (18,19). Our study revealed 1 (1.4%) patient who received urgent laparotomy because of hemorrhage following EC, in which hemostasis was successfully achieved. One patient (1.4%) in the EC group and one patient (3.4%) in the DC group developed intraabdominal fluid collections, who were treated by percutaneous drainage catheter application. One patient (1.4%) who underwent EC developed cystic stump leakage due to choledocholithiasis, which was then managed by stone extraction and plastic stent placement via ERCP. Apart from the aforementioned surgical complications, other postoperative complications included atelectasis in 1 (1.4%) patient and pulmonary embolism in another 1 (1.4%) patient in the EC group, whereas 1 (3.5%) patient in the DC group developed postoperative hyperbilirubinemia, all of whom were medically managed without any interventions. No statistically significant difference was found between the subgroups regarding overall complications ($p>0.05$).

A meta-analysis that was conducted by Wu et al. (20) reported that patients in the EC group had a shorter length

of hospital stay, yet longer operative times. Our study revealed that the mean length of hospital stay of the EC group was statistically longer than the DC group ($p<0.05$). Apart from the surgical complications, a longer hospital stay was attributed to the prolonged waiting period for the improvement of patients' clinical conditions and laboratory findings due to the systemic inflammatory reaction of AC before their perioperative periods.

Study Limitations

A limitation of our study included the relatively low number of patients and its single-center, cross-sectional study design. Contrarily, operating the patients in the EC group within the first week of their index hospitalization, regardless of the day from the onset of symptoms, can be attributed as the unique feature of our study.

Of the two main issues that were addressed in the 2016 guidelines of The World Society of Emergency Surgery, the first one is that surgery is clinically superior to follow-up, and the second is that cholecystectomy is considered the gold standard treatment of AC (21). Our findings recommend performing EC regardless of the onset of symptoms in the absence of confounding factors, such as poor clinical status, altered laboratory findings, advanced age, or comorbidities, which preclude surgical treatment for patients who are hospitalized with AC.

CONCLUSION

The surgical treatment of hospitalized patients with AC can safely be performed anytime within the first week of their admissions regardless of the time from the onset of symptoms unless the clinical and laboratory findings render the patient unfit for surgery. Therefore, achieving a definitive treatment at once is possible, without the need for further hospitalization. The findings of our study might suggest a paradigm shift regarding the "first 72-96 hours" requirement for cholecystectomy in AC cases.

ETHICS

Ethics Committee Approval: This study was approved by the Institutional Review Ethics Committee of Istanbul Medeniyet University Göztepe City Hospital (IRB: 2019/0327).

Informed Consent: Signed informed consent forms were obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: Ö.E., T.E., A.G., D.B., M.L., O.A., Concept: Ö.E., T.E., A.G., N.B., O.A., Design: Ö.E., T.E., O.A., Data Collection or Processing: Ö.E., T.E., A.G., N.B., M.L., O.A., Analysis or Interpretation: Ö.E., T.E., A.G., D.B., N.B., M.L., O.A., Literature Search: Ö.E., T.E., A.G., D.B., M.L., Writing: Ö.E., T.E., A.G., D.B., N.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. Wakabayashi G, Iwashita Y, Hibi T, Takada T, Strasberg SM, Asbun HJ, et al. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:73-86.
2. Gollan JL, Bulkley GB, Diehl AM, Elashoff JD, Federle MP, Hogan WJ, et al. Gallstones and laparoscopic cholecystectomy. JAMA 1993;269:1018-24.
3. Friedman GD. Natural history of asymptomatic and symptomatic gallstones. Am J Surg 1993;165:399-404.
4. Mou D, Tesfasilassie T, Hirji S, Ashley SW. Advances in the management of acute cholecystitis. Ann Gastroenterol Surg 2019;3:247-53.
5. Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. J Clin Epidemiol 1989;42:127-36.
6. Ko CW, Lee SP. Gastrointestinal disorders of the critically ill. Biliary sludge and cholecystitis. Best Pract Res Clin Gastroenterol 2003;17:383-96.
7. Kaoutzanis C, Davies E, Leichtle SW, Welch KB, Winter S, Lampman RM, et al. Abdominal ultrasound versus hepato-imino diacetic acid scan in diagnosing acute cholecystitis--what is the real benefit? J Surg Res 2014;188:44-52.
8. Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2013;20:35-46.
9. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:41-54.
10. Gurusamy KS, Davidson C, Gluud C, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database Syst Rev 2013;6:CD005440. doi: 10.1002/14651858.CD005440.pub3
11. Okamoto K, Suzuki K, Takada T, Strasberg SM, Asbun HJ, Endo I, et al. Tokyo Guidelines 2018: flow chart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci 2018;25:55-72.
12. Haisley KR, Hunter JG. Gallbladder and the extrahepatic biliary system. In: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Kao LS, et al, editors. Schwartz's Principles of Surgery, 11th ed. New York: McGraw Hill; 2019. p. 1393-427.
13. Gallagher TK, Kelly ME, Hoti E. Meta-analysis of the cost-effectiveness of early versus delayed cholecystectomy for acute cholecystitis. BJS Open 2019;3:146-52.
14. Gomes CA, Junior CS, Di Saverio S, Sartelli M, Kelly MD, Gomes CC, et al. Acute calculous cholecystitis: Review of current best practices. World J Gastrointest Surg 2017;9:118-26.
15. Jensen KK, Roth NO, Krarup PM, BardramL. Surgical management of acute cholecystitis in a nationwide Danish cohort. Langenbecks Arch Surg 2019;404:589-97.

16. Yi NJ, Han HS, Min SK. The safety of a laparoscopic cholecystectomy in acute cholecystitis in high-risk patients older than sixty with stratification based on ASA score. Minim Invasive Ther Allied Technol 2006;15:159-64.
17. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 2010;97:141-50.
18. Livingston EH, Rege RV. A nationwide study of conversion from laparoscopic to open cholecystectomy. Am J Surg 2004;188:205-11.
19. Lawrentschuk N, Hewitt PM, Pritchard MG. Elective laparoscopic cholecystectomy: implications of prolonged waiting times for surgery. ANZ J Surg 2003;73:890-3.
20. Wu XD, Tian X, Liu MM, Wu L, Zhao S, Zhao L. Meta-analysis comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 2015;102:1302-13.
21. Ansaloni L, Pisano M, Coccolini F, Peitzmann AB, Fingerhut A, Catena F, et al. 2016 WSES guidelines on acute calculous cholecystitis. World J Emerg Surg 2016;11:25.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:320-326
DOI: 10.4274/BMJ.galenos.2021.85047

Research

Treatment Outcomes in Hairy Cell Leukemia: Data of Patients in a Tertiary Referral Hospital in Turkey for Over 20 Years

Tüylü Hücreli Lösemide Tedavi Sonuçları: Türkiye'deki Üçüncü Basamak Bir Hastanede 20 Yıldan Fazla Hastaya Ait Veriler

Esma Evrim Doğan[1], Naciye Demirel[1], Esra Turan Erkek[2], Demet Aydın[1], İlknur Mansuroğlu[3], Melda Cömert Özkan[4], Rafet Eren[1]

[1]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Hematology, Istanbul, Turkey
[2]University of Health Sciences Turkey, Kartal Lütfü Kırdar City Hospital, Clinic of Hematology, Istanbul, Turkey
[3]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Pathology, Istanbul, Turkey
[4]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Hematology, Ankara, Turkey

ABSTRACT

Objective: To share our clinical experience on the first, second, and third-line treatments of hairy cell leukemia (HCL), with cladribine and other methods, including splenectomy and interferon treatments.

Methods: The clinical features, treatments (including response and complications), and survival data of 24 patients, who were diagnosed with HCL at Okmeydanı Training and Research Hospital between November 1996 and August 2019, were retrospectively analyzed.

Results: The mean follow-up time was 130.77±75.07 months. All patients who had received cladribine as a first-line treatment (n=17) demonstrated response to treatment, whereas complete response (CR) was observed in 41.2%. Mean progression-free survival after the first-line treatment was 83.58±57.40 months and median survival was 75.25 months (minimum-maximum: 2.14-194.79). Progression-free survival time was significantly longer in cladribine recipients.

Conclusion: The effectiveness of cladribine in HCL treatment was once more shown in this study; however, the low frequency of CR to cladribine in our study compared to the literature was considered to be related to the increased frequency of massive splenomegaly and lymphadenopathy at the time of diagnosis, as well as low platelet values.

Keywords: Cladribine, hairy cell leukemia, treatment, survival

ÖZ

Amaç: Tüylü hücreli löseminin (HCL) kladribin ve splenektomi ile interferon tedavileri gibi diğer yöntemlerle birinci, ikinci ve üçüncü basamak tedavileriyle ilgili klinik deneyimimizi paylaşmaktır.

Gereç ve Yöntem: Okmeydanı Eğitim ve Araştırma Hastanesi'nde Kasım 1996 ile Ağustos 2019 tarihleri arasında HCL tanısı alan 24 hastanın klinik özellikleri, tedavileri (yanıt ve komplikasyonlar dahil) ve sağkalım verileri geriye dönük olarak incelendi.

Bulgular: Ortalama takip süresi 130,77±75,07 aydı. Birinci basamak tedavi olarak kladribin alan tüm hastalar (n=17) tedaviye yanıt gösterdi ve %41,2'sinde tam yanıt gözlendi. İlk basamak tedaviden sonra ortalama progresyonsuz sağkalım 83,58±57,40 aydı ve medyan sağkalım 75,25 aydı (en küçük-en büyük: 2,14-194,79). Kladribin kullanan hastalarda progresyonsuz sağkalım süresinin anlamlı düzeyde daha uzun olduğu bulunmuştur.

Sonuç: Bu çalışmada kladribinin HCL tedavisinde etkinliği bir kez daha gösterilmiş olsa da, kladribine tam yanıt sıklığının literatüre göre düşük olması, tanıdaki masif splenomegali ve lenfadenopati sıklığının fazla olması ve düşük trombosit değeri ile ilişkili olduğu düşünülmüştür.

Anahtar Kelimeler: Kladribin, tüylü hücreli lösemi, tedavi, sağkalım

Address for Correspondence: Esma Evrim Doğan, University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Hematology, Istanbul, Turkey
Phone: +90 533 029 17 99 E-mail: md.esmaevrimdogan@outlook.com ORCID ID: orcid.org/0000-0003-0635-2966

Cite as: Evrim Doğan E, Demirel N, Turan Erkek E, Aydın Demet, Mansuroğlu İ, Cömert Özkan M, Eren R. Treatment Outcomes in Hairy Cell Leukemia: Data of Patients in a Tertiary Referral Hospital in Turkey for Over 20 Years. Med J Bakirkoy 2021;17:320-326

Received: 20.05.2021
Accepted: 16.10.2021

INTRODUCTION

Hairy cell leukemia (HCL) is a B cell lymphoproliferative disease that originates from postgerminal central memory cells and splenic marginal zone B cells and is characterized by pancytopenia, splenomegaly, bone marrow involvement accompanied by fibrosis, and the presence of lymphoid cells with cytoplasmic extension (hair-like) in the peripheral blood (1,2). The characteristic immunophenotype of cluster of differentiation (CD)19+, CD20+, CD11c+, CD25+, CD103+, and CD123+ co-expressing cells confirms the diagnostic features of HCL classic. HCL constitutes 2% of all adult leukemias (3). Apart from childhood, the disease can develop in all ages, but is often diagnosed in Caucasian males over 50 years old (4 times more common compared to females) (1,3).

HCL usually progresses very slowly and current therapies achieve high levels of success (4). Patients who are asymptomatic without progression are followed up without treatment, whereas those symptomatic and those who meet cytopenia criteria receive treatment through a well-defined algorithm of first- and second-line therapy, which includes the use of cladribine (2-chlorodeoxyadenosine, 2CdA) and pentostatin (deoxycoformycin). Additional treatment options include splenectomy, interferon-alpha (IFN-α), and chemotherapy, especially as second-line therapy (5). After the introduction of purine analogs (cladribine and pentostatin) as treatment options for HCL, complete remission was demonstrated to be obtained in approximately 75% of patients, and despite possible relapse within 15 years (50% of patients), most individuals are likely to have a near-normal life expectancy (6-8).

This retrospective study aimed to analyze the treatment response and adverse effects of treatment, relapses, survival, and occurrence of secondary malignancies in our center during the 24 years of follow-up.

METHODS

Study Group and Evaluation

The study group was comprised of all individuals diagnosed with HCL at Okmeydanı Training and Research Hospital between November 1996 and August 2019. The patients diagnosed with hairy cell variants and those with missing medical files were excluded from the study. Demographic data, clinical features, and treatment-related characteristics and outcomes of 24 patients were recorded from the files and were retrospectively analyzed within the scope of the study.

Bone marrow biopsy results were categorized based on infiltration type (interstitial, diffuse, and both) and degree of fibrosis (scored on a scale from 0 to 4) (9).

Definitions, Treatment Approach, and Response Evaluation

HCL diagnosis was made according to the World Health Organization criteria based on the results of flow cytometry or bone marrow morphology and immunohistochemistry (10). Treatment is generally initiated in patients with significant cytopenia [Hemoglobin (Hb) of <11 g/dL, ANC] of $<1{\cdot}0 \times 10^9$/L, and/or platelets of $<100 \times 10^9$/L), massive or symptomatic splenomegaly, constitutional symptoms (such as fever or night sweats), and/or infections (11).

Splenectomy, IFN-α (referred to as IFN henceforth), cladribine, and rituximab were the treatment options utilized during the 24 years. IFN and splenectomy were preferred as first-line therapy when cladribine was unavailable in Turkey. IFN was started at a dosage of 3 MU three times a week. Splenectomy was performed either laparoscopically or via open surgery. Cladribine was given either by continuous intravenous infusion at 0.1 mg/kg/day (1-7 days), 2-hour intravenous infusion at 0.1 mg/kg for 5 consecutive days or once a week for 7 consecutive weeks, or subcutaneously at 0.14 mg/kg/day for 5 days (12). Rituximab was administered at 375 mg/m^2 weekly for four consecutive weeks (13).

The response was evaluated by complete blood count, peripheral blood smear, biochemical parameters, and bone marrow biopsy at 3 months after therapy initiation. Complete response (CR) was defined as (1) the disappearance of hairy cells in the peripheral blood smear and bone marrow, (2) absolute neutrophil count of $>1{,}500 \times 10^6$/L, platelet of $>100 \times 10^9$/L, and Hb of >11 gr/dL, and (3) splenomegaly regression on physical examination. Partial response (PR) was defined as near-normalization of the peripheral blood count (as in CR) with a minimum of 50% improvement in organomegaly and bone marrow biopsy infiltration with HCL. Relapse was defined as a reappearance of hairy cells in peripheral blood or bone marrow and recurrence of the previously mentioned types of cytopenia or organomegaly or >50% increased residual disease after PR. The presence of PR or CR was included in the overall response (OR) evaluations. Any response rather than PR or CR was regarded as no response (14,15).

The overall survival was defined as the time from HCL diagnosis until the death of any cause or the date of the last observation. Relapse-free survival was defined as the time from the treatment initiation until relapse or death, and patients who remained disease-free were censored at the date of the last observation.

Ethics

All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Clinical Research Ethics Committee of Medical Sciences University, Okmeydanı Training and Research Hospital (approval no: 1387). Informed written consent was obtained from all individual participants who are included in the study.

Statistical Analysis

The Number Cruncher Statistical System 2007 software was used for all statistical analyses. Research data evaluating presented the descriptive statistics with mean, standard deviation, median, and minimum and maximum values for quantitative data, whereas frequency and percentage were used for categorical data. The Kaplan-Meier survival analysis was used for the survival analyses. The threshold for statistical significance was set at $p<0.05$.

RESULTS

A total of 24 patients with a median age of 53.5 years were included in the study, wherein 4 (16.7%) were female and 20 (83.3%) were male. Twelve (50%) of the patients were incidentally detected and were asymptomatic at the time of diagnosis despite having cytopenia. The characteristics and the presenting features of patients are listed in Table 1.

The laboratory tests evaluation detected neutropenia in 18 patients (66.7%), pancytopenia in 14 patients (58.3%). In addition, monocytopenia was detected in 8 patients (33.3%) out of the 18 patients with available measurements (Table 2). Biopsy findings on bone marrow evaluations are presented in Table 3.

All 24 patients required treatment at presentation, including patients who are asymptomatic but required treatment due to cytopenia. Cladribine was administered to 17 (70.8%) as first-line therapy, wherein 7 (41.2%) had CR and 10 (58.8%) had PR. Five patients were given IFN therapy as first-line treatment, wherein 1 patient remained unresponsive and 4 patients had PR. Finally, splenectomy was performed as the first-line therapy in 2 patients, one of which partially responded, whereas the other patient did not attend follow-up and applied with a relapse later on.

Only 1 (16.7%) of the 6 patients with CR to cladribine as the first-line treatment required second-line treatment after 4 years. Among the 10 patients with PR to cladribine, 4 required second-line treatment 6-10 years after initial treatment.

Table 1. Characteristics and presenting features of patients with hairy cell leukemia

	N	(%)
Median age	53.5 (35-78)	
Sex		
Female	4	(16.7)
Male	20	(83.3)
B symptoms	3	(12.5)
Weight loss	2	(8.3)
Night sweating	1	(4.2)
Fever	1	(4.2)
Malaise	5	(20.8)
Fever and infection	3	(12.5)
Abdominal pain	3	(12.5)
Bleeding	3	(12.5)
Ecchymosis	3	(12.5)
Gingival bleeding	1	(12.5)
Hematuria	1	(4.2)
Abdominal swelling	2	(8.3)
Splenomegaly		
No	2	(8.3)
Yes	22	(91.7)
Mean spleen size, cm	20.30	±5.58 cm
Massive splenomegaly	10	(41.7)
Hepatomegaly		
No	11	(47.8)
Yes	12	(52.2)
Lymphadenopathy		
No	18	(75.0)
Yes	6	(25.0)
Peripheral	1	(16.7)
Mediastinal	4	(66.7)
Abdominal	3	(50.0)
Positive staining		
CD20	19	(82.6)
CD103	8	(34.8)
CD11c	11	(47.8)
CD19	6	(26.1)
CD25	5	(20.8)
CD38	1	(4.2)

CD: Cluster of differantiation

Table 2. The distribution of peripheral blood parameters

	Median (minimum-maximum)
Hemoglobin	8.77 (4.8-13.8)
Platelet	48,500 (2,000-151,000)
Leukocyte	2,945 (1,200-37,940)
Absolute neutrophil count	600 (100-3,790)
Monocyte count	510 (50-29,900)
Hairy cell quantification in peripheral blood	17 (8-50)
	N
Hairy cell in peripheral blood	
No	18
Yes	6

Table 3. Bone marrow biopsy findings

	N	(%)
Infiltration type	24	(100)
Diffuse	12	(50.0)
Interstitial	7	(29.2)
Diffuse + interstitial	3	(12.5)
Unknown	2	(8.3)
Degree of fibrosis	24	(100)
Not checked	2	(8.3)
1/4	2	(8.3)
2/4	11	(45.83)
3/4	9	(37.5)
TRAP positivity	24	(100)
Unchecked	1	(8.3)
Positive	23	(91.7)

TRAP: Tartrate-resistant acid phosphatase

Overall progression-free survival after first-line therapy was 83.58±57.40 months. In cases where cladribine was administered, 12 (70.6%) were progression-free and 5 had a relapse and the mean progression-free survival time was 142.91±16.69 months. In cases where cladribine was not administered, 1 patient (14.3%) was progression-free and 6 had a relapse and the mean progression-free survival time was 78.07±24 months. The progression-free survival analysis via the log-rank test revealed a significantly shorter progression-free survival rate in patients who did not receive cladribine as first-line therapy ($p<0.001$).

A total of 11 patients received second-line therapy. Ten patients received cladribine, of which 6 (60%) had CR and 4 (40%) had PR. The overall median progression-free survival time after the second-line therapy was 126.39 months, whereas 73.8 months for cladribine recipients.

Among 2 patients who had PR to cladribine therapy in the second-line treatment, 1 was given rituximab with CR, whereas cladribine therapy was repeated in the other, which resulted in PR (Table 4).

Approximately 2 years after IFN treatment, 1 patient who was partially responsive developed osteomyelitis. Four of the patients (16.67%) had concomitant malignancy (basal-cell carcinoma, ureteral adenocarcinoma, laryngeal adenocarcinoma, and prostatic adenocarcinoma), wherein 1 was detected before treatment (prostatic adenocarcinoma), secondary malignancy was detected in 2 patients after cladribine treatment and 1 after IFN therapy.

As a complication of cladribine treatment, 5 patients developed febrile neutropenia and responded to antibiotherapy and G-CSF treatment. Two of the patients died due to concomitant secondary malignancies. As of writing, 22 of the 24 patients (91.7%) are still alive. Overall, the final data showed that mean survival was 132.58±16.98 months and mean follow-up duration was 130.77±75.07 months (Table 5, Figure 1-3).

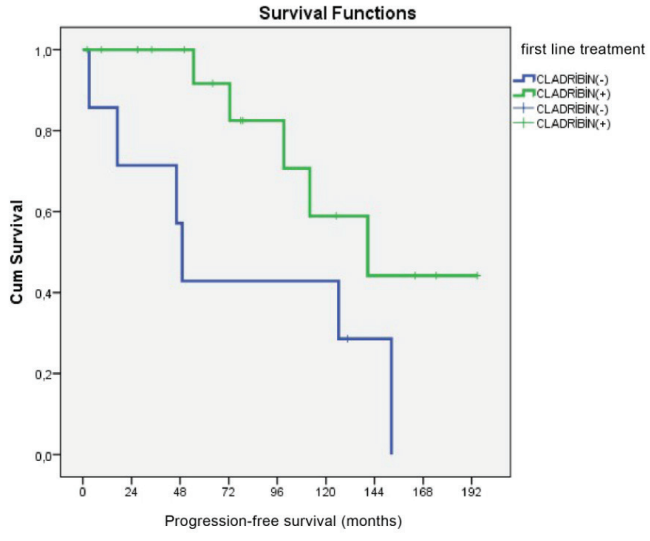

Figure 1. Kaplan-Meier curve of progression-free survival according to cladribine used in first-line treatment

DISCUSSION

The current study provides additional data demonstrating the efficacy of available treatment modalities in patients

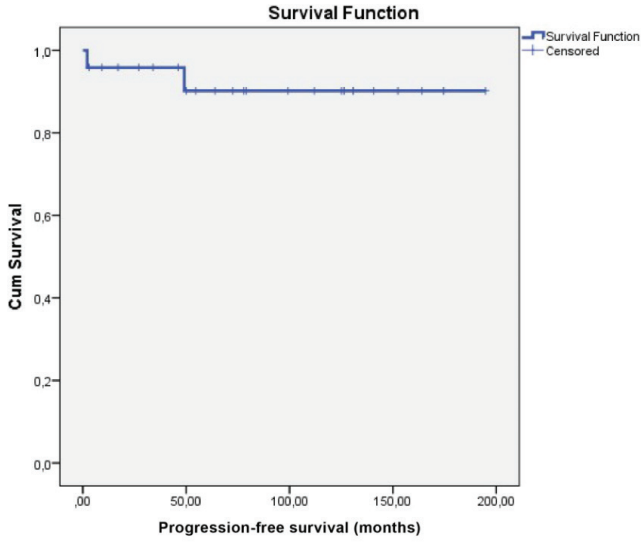

Figure 2. Kaplan-Meier curve of progression-free survival after first and second-line treatment

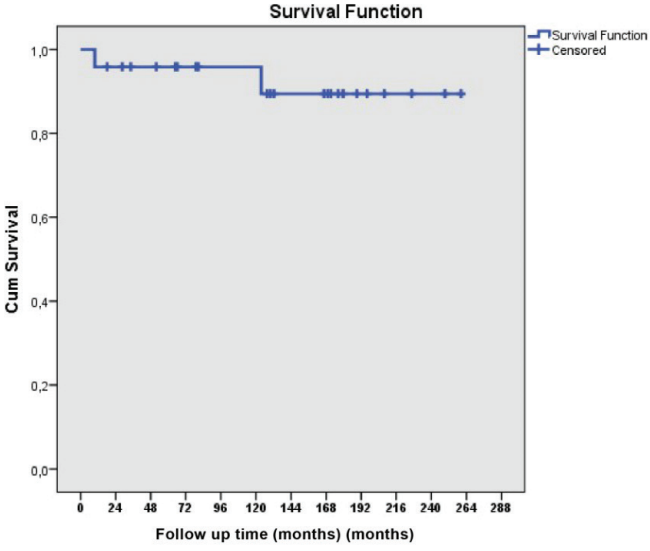

Figure 3. Kaplan-Meier curve for overall survival

with HCL, especially for cladribine therapy that yielded a significantly longer progression-free survival and reduced the frequency of relapse compared to patients who had not received cladribine as first-line therapy. Of note, all patients responded to cladribine; however, CR was observed in only 41.2% of patients.

The study conducted by Mikler Mascarenhas (7) (12 patients) revealed a treatment response to cladribine from all participants, and the CR rate was 92%. The literature reported frequencies ranging from 75% to 100% CR to cladribine in large-scale series (16,17). This situation was attributed to the presence of severe thrombocytopenia, massive splenomegaly, or multiple lymphadenopathies in our cases.

The literature focusing on the clinical findings of patients with HCL show that the most frequently identified examination findings are splenomegaly (60-90%) and cytopenia (anemia, leukopenia, neutropenia, thrombocytopenia, and monocytopenia with frequencies of 70%, 65%, 75%, 80%, and 90%, respectively) (14,18,19). Our study found anemia in 91.7% of patients, leukopenia in 62.5%, neutropenia in 66.7%, thrombocytopenia in 95.8%, and monocytopenia in 33.3%. Findings other than monocytopenia were very similar in frequency to values reported in the literature. The lower frequency of monocytopenia may be in part due to the initial monocyte levels that were not determined in 6 patients. Even so, tartrate-resistant acid phosphatase positivity was present in 100% of our patients and all were diagnosed with typical HCL; therefore, even if all of these 6 individuals had monocytopenia, there would still be a considerable difference compared to studies reporting data from patients with typical HCL.

In the 2000 update of the HCL guideline published by the British Society for Hematology, the severity of cytopenia was reported to depend on spleen size and extensive bone marrow infiltration (20). Pancytopenia was determined in 14 of our patients (58.3%), 22 (91.7%) had splenomegaly, and 15 (62.5%) had diffuse bone marrow infiltration. Pancytopenia and splenomegaly ratios in our study are very similar to those reported by Chatterjee et al. (21); however, their results are higher than those reported in other literature (2,4).

Lymphadenopathy was detected in 25% (n=6) of our 24 patients, and it was reported to be within 9%-20% in the literature (4,6,21-23). In our series, 3 patients had mediastinal, 2 had intra-abdominal multiple lymphadenopathies, and 1 had extensive and conglomerate lymphadenopathy. In another patient, extensive lymphadenopathy involvement was observed in the axillary, mediastinal, and intra-abdominal regions. All three patients with mediastinal lymphadenopathy partially responded to cladribine treatment. These lymph nodes were not extensively affected (and did not exceed 2 cm), which suggests that mediastinal localization may have a negative effect on treatment response. Among the patients with extensive multiple intra-abdominal lymphadenopathies, those with extensive conglomerate lymphadenopathy partially responded to cladribine, whereas the others demonstrated CR. This suggests that the extent and size of the intra-abdominal lymph node involvement may be more important than localization. Indeed, in a study of 88 cases in which Mercieca et al. (24) investigated the frequency of abdominal lymphadenopathy in HCL, the presence of abdominal lymphadenopathy was found to be associated

Table 4. Distribution of first-line treatments and treatment response

First-line treatments	Interferon α (n=5, 20.8%)	Cladribine (n=17, 70.8%)	Splenectomy (n=2, 8.3%)	Total (n=24, 100%)
Unresponsive, n (%)	1 (20%)	0	0	1 (4.2%)
Partial response, n (%)	4 (80%)	10 (58.8%)	1 (50%)	15 (62.5%)
Complete response, n (%)	0	7 (41.2%)	0	7 (29.2%)
No follow-up, n (%)	0	0	1 (50%)	1 (4.2%)

Table 5. Survival analyses according to the use of cladribine as first-line treatment

	Cladribine (+) (n=17, 70.8%)	Cladribine (-) (n=7, 29.2%)	p
Patients with relapse	5 (29.4%)	6 (85.7%)	0.012
Patients with progression-free survival	12 (70.6%)	1 (14.3%)	
Mean progression-free survival, months	142.91±16.69	78.07±24.53	<0.001

with treatment resistance. In an earlier publication by the same author that included 12 cases with HCL who had abdominal lymphadenopathy, abdominal imaging was stated to be necessary at the time of diagnosis (25).

No staging system for HCL has yet been defined in the literature. However, considering that our patients had more frequent splenomegaly and pancytopenia at presentation, the increased frequency and the extent of lymphadenopathy involvement may suggest that patients were admitted with relatively advanced disease. However, larger case series need to be evaluated to define "advanced disease" and to claim that lymph node involvement may be more frequent in such patients. These studies will also be important to determine whether the localization of lymphadenopathy has any influence on treatment response.

Similar to the study of Öngören et al. (26), our study found a significantly lower frequency of progressive disease in patients who received cladribine as first-line treatment compared to those who received splenectomy or IFN treatment. The mean follow-up time of patients was 130.77±75.07 months, the mean progression-free survival after the first-line cladribine treatment was 142.91±16.69 months (median: 77.96 months). These values were found to be longer than those reported by other domestic studies, but shorter than that of the 233-case study by Else et al. (27) (6,26). After the second-line therapy, the OR to cladribine was again 100%, while the CR rate was 60%. Higher CR rates after relapse were thought to be due to a lower frequency of lymph node involvement and massive splenomegaly at the time of relapse. Mean progression-free survival after second-line treatment was 83.45±66.82 months (median 73.8 months), again shorter compared to the study by Else et al. (27); however, studies have repeatedly shown that severe anemia and severe thrombocytopenia are associated with decreased survival (17). Therefore, the difference may be due to the presence of higher median hemoglobin and platelet levels at the time of diagnosis in the study by Else et al. (27).

The rarity of HCL, the single-center nature of our data, and the number of patients included in the study are notable limitations, which must be considered when concluding our results. Furthermore, even though clinical data deficits were minimal, the presence of missing data and the insufficient measurements in all patients may further hamper the accuracy of laboratory-related findings.

CONCLUSION

Finally, the lack of β2-microglobulin and BRAF mutation analysis is an important limitation.

Such high lymph node involvement at the time of diagnosis in our group of patients seems remarkable, and therefore, is believed to be a factor that reduced cladribine response. The effects of the presence of abdominal multiple lymphadenopathies, occurring particularly due to relapse, on the treatment response has been investigated in the literature; however, large-scale studies are needed to evaluate the effects of extensive lymph node involvement and its localization in the early phase, especially for its influence on therapy response and survival.

ETHICS

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Medical Sciences University, Okmeydani Training and Research Hospital (approval no: 1387).

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

Authorship Contributions

Surgical and Medical Practices: E.E.D., D.A., R.E., Concept: E.E.D., N.D., D.A., Design: E.E.D., İ.M., R.E., Data Collection

or Processing: N.D., E.T.E., M.C.Ö., Analysis or Interpretation: E.T.E., D.A., M.C.Ö., Literature Search: E.E.D., N.D., E.T.E., İ.M., Writing: E.E.D., N.D., İ.M., R.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. Robak T, Matutes E, Catovsky D, Zinzani PL, Buske C; ESMO Guidelines Committee. Hairy cell leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v100-7.
2. Troussard X, Cornet E. Hairy cell leukemia 2018: Update on diagnosis, risk-stratification, and treatment. Am J Hematol 2017;92:1382-90.
3. Gürman G. Lenfoplazmasitik Lenfoma. HematoLog: Türk Hematoloji Derneği 2013;3:271-5.
4. Somasundaram V, Purohit A, Aggarwal M, Manivannan P, Mishra P, Seth T, et al. Hairy cell leukemia: A decade long experience of North Indian Hematology Center. Indian J Med Paediatr Oncol 2014;35:271-5.
5. Lauria Af G, Raspadori D. The Therapy of Hairy Cell Leukemia: The State of Art. Ann Hematol Oncol 2015;2:1035.
6. Erkut N, Batur DS, Akidan O, Karabacak V, Sönmez M. Tüylü Hücreli Lösemili Hastaların Uzun Dönem Tedavi Sonuçları: Tek Merkez Deneyimi. Türkiye Klinikleri Tip Bilimleri Dergisi 2018;38:236-40.
7. Mikler E, Mascarenhas J. Current therapeutic options in hairy cell leukemia. J Community Support Oncol 2014;12:104-8.
8. Liu Q, Harris N, Epperla N, Andritsos LA. Current and Emerging Therapeutic Options for Hairy Cell Leukemia Variant. Onco Targets Ther 2021;14:1797-805.
9. Bain BJ, Clark DM, Wilkins BS. Bone marrow pathology: John Wiley & Sons, 2019.
10. Norris D, Stone J. WHO classification of tumours of haematopoietic and lymphoid tissues. Geneva: WHO. 2008:188-90.
11. Thompson PA, Ravandi F. How I manage patients with hairy cell leukaemia. Br J Haematol 2017;177:543-56.
12. Benz R, Arn K, Andres M, Pabst T, Baumann M, Novak U, et al. Prospective long-term follow-up after first-line subcutaneous cladribine in hairy cell leukemia: a SAKK trial. Blood Adv 2020;4:3699-707.
13. Leclerc M, Suarez F, Noël MP, Vekhoff A, Troussard X, Claisse JF, et al. Rituximab therapy for hairy cell leukemia: a retrospective study of 41 cases. Ann Hematol 2015;94:89-95.
14. Grever MR, Abdel-Wahab O, Andritsos LA, Banerji V, Barrientos J, Blachly JS, et al. Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia. Blood 2017;129:553-60.
15. Andrasiak I, Rybka J, Wrobel T. Response to the Therapy in Hairy Cell Leukemia: Systematic Review and Meta-Analysis. Clin Lymphoma Myeloma Leuk 2018;18:392-9.e3.
16. Maevis V, Mey U, Schmidt-Wolf G, Hairy cell leukemia: short review, today's recommendations and outlook. Blood Cancer J 2014;4:e184.
17. Grever MR. How I treat hairy cell leukemia. Blood 2010;115:21-8.
18. Delrieu V, Springael C, Wu K, Verhoef G, Janssens A. BHS guidelines for the diagnosis and the treatment of hairy cell leukaemia. Belg J Hematol 2017;8:222-8.
19. Parry-Jones N, Joshi A, Forconi F, Dearden C; BSH guidelines committee. Guideline for diagnosis and management of hairy cell leukaemia (HCL) and hairy cell variant (HCL-V). Br J Haematol 2020;191:730-7.
20. Catovsky D. On behalf of the Clinical Task Force of the British Committee for Standards in Haematology. Hairy cell leukaemia. Guidelines on diagnosis and therapy. 2000.
21. Chatterjee T, Panigrahi I, Mahapatra M, Pati HP, Kumar R, Naithani R, et al. Hairy cell leukemia: clinical, pathological and ultrastructural findings in Asian-Indians. Indian J Cancer 2008;45:41-4.
22. Hilmi Erdem G, Vildan O, Zafer Serenli Y, Vildan G, Ridvan A, Fahir O. Hairy Cell Leukemia: A Single-Center Experience. LLM Dergi 2017;1:85-91.
23. Matutes E. Diagnostic and therapeutic challenges in hairy cell leukemia-variant: where are we in 2021? Expert Rev Hematol 2021;14:355-63.
24. Mercieca J, Puga M, Matutes E, Moskovic E, Salim S, Catovsky D. Incidence and significance of abdominal lymphadenopathy in hairy cell leukaemia. Leuk Lymphoma 1994;14 Suppl 1:79-83.
25. Mercieca J, Matutes E, Moskovic E, MacLennan K, Matthey F, Costello C, et al. Massive abdominal lymphadenopathy in hairy cell leukaemia: a report of 12 cases. Br J Haematol 1992;82:547-54.
26. Öngören Ş, Eşkazan AE, Berk S, Elverdi T, Salihoğlu A, Ar MC, et al. Retrospective Evaluation of Hairy Cell Leukemia Patients Treated with Three Different First-Line Treatment Modalities in the Last Two Decades: A Single-Center Experience. Turk J Haematol 2017;34:291-9.
27. Else M, Dearden CE, Matutes E, Garcia-Talavera J, Rohatiner AZ, Johnson SA, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. Br J Haematol 2009;145:733-40.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:327-333
DOI: 10.4274/BMJ.galenos.2021.58569

Research

Correlation Between Computerized Tomography Findings and DeMeester Score and Esophagogastroduodenoscopy Findings in Patients with GERD-like Symptoms

GERH Benzeri Semptomları Olan Hastalarda Bilgisayarlı Tomografi Bulguları ile DeMeester Skoru ve Özofagogastroduodenoskopi Bulguları Arasındaki İlişki

Hakan Yirgin[1], İnci Kızıldağ Yirgin[2], Süleyman Sönmez[3]

[1]University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Gastroenterology Surgery, Istanbul, Turkey
[2]Istanbul University Institute of Oncology, Department of Radiology, Istanbul, Turkey
[3] University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey

ABSTRACT

Objective: Radiological imaging has a limited role in the initial diagnosis of gastroesophageal reflux disease (GERD) without complications. This study aimed to investigate the correlation with the presence of hiatal hernia (HH), the number of hiatal area pixels, the angle of His on computerized tomography (CT) imaging, esophagogastroduodenoscopy (EGD) findings, and DeMeester scores in patients with GERD-like symptoms.

Methods: This retrospective study included 46 consecutive patients with typical GERD-related symptoms. All patients underwent EGD examinations. Patients were divided into two groups as HH and hiatal insufficiency based on the EGD results. The DeMeester score of >14.72 was considered abnormal acid reflux, whereas <14.72 was normal. Anatomical details of esophageal hiatus on CT were separately recorded.

Results: A statistically significant correlation was found between EGD and CT imaging findings using the Pearson correlation test ($p<0.05$). No statistically significant difference was found between the number of hiatal area pixels and DeMeester scores using the Mann-Whitney U test ($p=0.49$). No statistically significant difference was found between the angle of His and DeMeester scores using the Mann-Whitney U test ($p=0.45$).

Conclusion: Anatomical details of esophageal hiatus are correlated with endoscopy findings in CT imaging.

Keywords: Gastroesophageal reflux, DeMeester score, endoscopy, hiatal hernia, pH-metry, tomography

ÖZ

Amaç: Radyolojik görüntüleme yöntemleri, komplikasyon gelişmemiş gastroözofageal reflü hastalığının (GERH) ilk tanısında sınırlı bir role sahiptir. Bu çalışmada, GERH tanısı bulunan hastalarda hiatal herni (HH) varlığı, hiatal alandaki piksel sayısı, bilgisayarlı tomografi (BT) görüntülemede His açısı, özofagogastroduodenoskopi (EGD) bulguları ve DeMeester skorları arasındaki korelasyonu araştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmaya tipik GERH ile ilgili semptomlarla başvuran 23 ila 74 yaşları arasındaki 46 hasta (medyan yaş 46, 24 erkek ve 22 kadın) dahil edildi. Tüm çalışma hastalarına EGD incelemeleri yapıldı. EGD sonuçlarına göre hastalar HH ve hiatal yetmezlik olarak iki gruba ayrıldı. DeMeester skorunun 14.72'den fazla olması anormal asit reflü, 14.72'den az olması normal sonuç olarak kabul edildi. BT'de özofagus boşluğunun anatomik detayları ayrı ayrı kaydedildi.

Bulgular: Pearson korelasyon testinde EGD bulguları ile BT görüntüleme bulguları arasında istatistiksel olarak anlamlı bir korelasyon vardı ($p<0,05$). Mann-Whitney U testinde hiatal alandaki piksel sayısı ile DeMeester skoru arasında istatistiksel olarak anlamlı bir fark saptanmadı ($p=0,49$). Benzer şekilde, Mann-Whitney U testinde His açısı ve DeMeester skoru arasında istatistiksel olarak anlamlı bir fark bulunmadı ($p=0,45$).

Sonuç: BT görüntülemede elden edilen özofagial hiatusa ait anatomik detaylar endoskopi bulguları ile korelasyon göstermektedir.

Anahtar Kelimeler: Gastroözofageal reflü, De Meester skoru, endoskopi, hiatal herni, pH-metri, tomografi

Address for Correspondence: İnci Kızıldağ Yirgin, Istanbul University Institute of Oncology, Department of Radiology, Istanbul, Turkey
Phone: +90 530 820 46 89 E-mail: incikizil@hotmail.com ORCID ID: orcid.org/0000-0003-0563-5964

Cite as: Yirgin H, Kızıldağ Yirgin İ, Sönmez S. Correlation Between Computerized Tomography Findings and DeMeester Score and Esophagogastroduodenoscopy Findings in Patients with GERD-like Symptoms. Med J Bakirkoy 2021;17:327-333

Received: 06.07.2021
Accepted: 19.11.2021

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal disease that affects 15-20% of people in the United States and 5% in Asia (1). A proper definition of GERD is very important for initiating efficacious therapy and avoiding esophageal problems, such as Barret's esophagus and adenocarcinoma. Cross-sectional imaging has an obvious role in GERD diagnosis and complication evaluation, as well as benign and malign lesion differentiation in staging and post-therapy evaluation of esophageal carcinoma (2). According to the American Gastroenterological Association guideline, esophagogastroduodenoscopy (EGD), of which symptoms do not decrease after proton pump inhibitor (PPI) treatment, is the most prevalent following step for a certain diagnosis and complication evaluation. The second step for patients with a suspected GERD syndrome, who have not responded to an empiric therapy of PPI, have normal results on endoscopy but without significant findings on manometry in pH monitoring (3).

Radiological imaging has a restricted role in primary GERD diagnosis without complications. Fluoroscopic esophagography has been routinely used by radiologists as a safe, available, and inexpensive method but is not advisable for GERD determination following the revised guidelines (4,5). Studies documented no correlation between barium esophagography with pH monitoring (6).

In recent years, cross-sectional radiological methods were more frequently used in patients with reflux symptoms to exclude cardiac and pulmonary differential diagnoses. This data accumulation prompted radiologists to radiologically evaluate the esophageal hiatus and gastroesophageal junction and investigate its correlation with symptoms. A few studies showed that dynamic magnetic resonance imaging (MRI) swallowing is an appropriate method to assess patients with gastroesophageal reflux complaints (7,8). One study evaluated the correlation between the distal esophageal wall thickness on computerized tomography (CT) and the presence of reflux esophagitis (RE), which found a moderate association (9). The importance of accurate measurements of esophageal hiatus in the preoperative period was noticed with increased anti-reflux surgeries. CT measurement of hiatal surface area has the potential to preoperatively guide decision-making in anti-reflux surgery technique, and the same methodology can be used to post-operatively assess surgical results. Yildirim et al. (10) measured the abdominal part of esophageal length (IAEL) and cardio-esophageal angle (COA) to identify patients with GERD in 2011. They revealed that the CT imaging method could be used for IAEL and COA measurements with a good degree of disease concordance (10). Koch et al. (11) published a study in 2012, wherein they investigated the association between the hiatal hernia (HH) size that was preoperatively measured and the esophageal hiatus size that was intraoperatively measured using the barium swallow imaging method. This study demonstrated a poor sensitivity of preoperative barium swallow examination, and surgeons could not rely on these imaging method findings (11). Ouyang et al. (12) published a study in 2016, wherein they measured the hiatal surface area on CT and showed evidence of hiatal HH associated with wide hiatuses and GERD. Additionally, their work revealed an inadequate hiatal surface area to determine GERD without CT findings (12).

To our knowledge, the correlation between DeMeester score and CT imaging measurement findings in patients with GERD-like symptoms has not been published. This study focused to research the correlation with the HH presence, the number of hiatal area pixels, the angle of His on CT imaging and EGD findings, and DeMeester scores in patients with GERD-like symptoms.

METHODS

Participants

This retrospective study included 46 consecutive patients aged 23 to 74 years (median age 46 years, 24 males and 22 females) who presented themselves in our surgical outpatient clinic with typical GERD-related symptoms. The hospital archive was searched between March 2019 and March 2020, which showed that 60 patients had CT scan, EGD, and 24 h esophageal pH-metry in less or equal to six months apart. Excluded from the study were 14 patients with inadequate clinical information or non-diagnostic CT scans. None of the patients were diagnosed with achalasia or scleroderma and none had prior gastrointestinal surgery. All patients had permanent or repetitive GERD symptoms despite therapy with PPI in at least 6 months. This study was approved by the Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (no: 15916306-604.01.01). All patients signed written informed consent before every medical examination.

Esophagogastroduodenoscopy

All study participants underwent upper gastrointestinal endoscopic examinations. Patients were classified into two groups as HH and hiatal insufficiency following the EGD results. The diagnostic criterion of endoscopic HH was accepted as the proximal dislocation of the gastroesophageal junction of >2 cm above the

diaphragmatic indentation. Hiatal insufficiency was defined when gastroesophageal junction at the normal location but presented with respiration-dependent incomplete closure of the cardi around the endoscope. Standard upper gastrointestinal endoscopy using the Fujinon (Fujifilm, light source XL-4450) video gastroduodenoscopies was done to determine the presence of macroscopic causes.

pH-metry/DeMeester Score

A 24-hour esophageal pH monitoring was applied with a catheter passing through the nasal cavity and located in the distal esophagus. A pH sensor of >5 cm from the level of the lower esophageal sphincter was fixed with the catheter and attached to a movable recorder tool for 24 h. After catheter placement, patients went to their homes and suggested doing normal routine jobs. The conventional DeMeester score was evaluated by a medical measurement system (MMS, UPS 2020, ORION II). DeMeester score includes these following parameters: the number of reflux events, the total duration of pH of<4 (%), duration of pH of<4 in vertical and horizontal positions (%), the number of reflux events >5 min, and the period of the major reflux event (13). A result of >14.72 was decided as acid reflux, whereas<14.72 was normal.

Imaging Analysis

CT images that are obtained based on different clinical symptoms, at most 6 months before EGD, were included in the study. All scans were obtained with a 16-slice CT scanner (Siemens Somatom Emotion, Siemens Medical Systems, Erlangen, Germany). Examinations that excluded the esophageal hiatus in the imaging area were excluded from the study. Non-contrast abdominal CT imaging for urinary symptoms was determined in 15 patients, whereas 8 had intravenous (IV) contrast-enhanced thorax CT imaging for pulmonary symptoms, and 23 had both IV and oral contrast-enhanced abdominal CT imaging due to upper abdominal pain. Before oral contrast examination, 1.5 l of diluted oral contrast material (76%, 50 mL of diatrizoic acid, Bayer-Schering Pharma, Seoul, Korea) was administered. IV injection of nonionic iodinated contrast (iohexol of 300 mg; Amersham Health, Cork, Ireland) was applied at a dosage of 1 mL/kg. Two radiologists with experience in abdominal radiology (6 and 4 years, respectively) evaluated the CT sections and did calculations. Esophagogastric junction localization was defined by esophageal tubular contour and angle of His changes. All CT scans were assessed for HH without quantitative definition with these parameters. Measurements were made using sagittal reformatted CT sections of the esophageal hiatus. A grading system devised by Ouyang et al. (12) was used to categorize patients as possible, probable, or definite HH. Our study used the same grading system and HH was considered present if the length of the hernia was >2 cm from the esophageal hiatus plane. Length between 1 and 2 cm was determined as probable HH and length between 0 and 1 cm was determined as possible HH (Figure 1). The number of hiatal area pixels was measured on axial CT sections using ImageJ software (National Institutes of Health, USA). ImageJ version 1.46 is a free accessible software program that was created by the National Institutes of Health for image postprocessing and evaluation (downloadable from http://rsbweb.nih.gov/ij/download.html). The hiatal areas were manually drawn. The number of pixels in the drawn areas was calculated with this program (Figure 2). The angle of His was measured on coronal CT reformatted images by two lines formed to the right wall of the gastric fornix and abdominal esophageal wall (Figure 1).

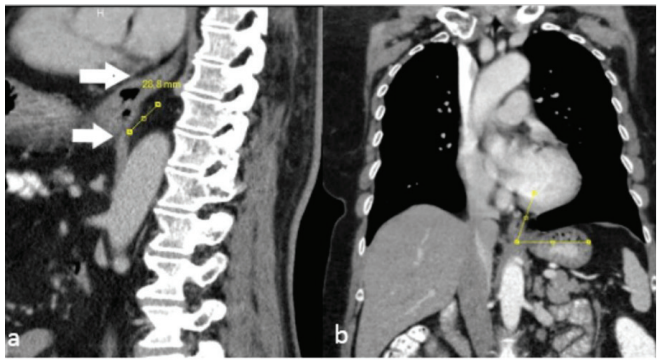

Figure 1. a) Sagittal CT sections of the esophageal hiatus shows definite HH, Length of the hernia at 2 cm above (superior arrow) the level of the esophageal hiatus (inferior arrow). b) Coronal CT images of the esophageal hiatus shows the angle of His that formed by the abdominal esophageal wall and the right wall of the gastric fornix
CT: Computerized tomography, HH: Hiatal hernia

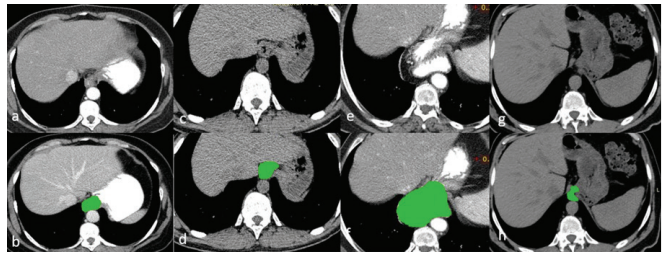

Figure 2. a,b) a 60-year-old female patient presented with axial CT images passing through the level of the esophageal hiatus. The number of pixels in the green area was calculated as 937. c,d) a 28-year-old male patient presented with axial CT images passing through the level of the esophageal hiatus. The number of pixels in the green area is calculated as 903. e,f) a 63-year-old female patient presented with axial CT images passing through the level of the esophageal hiatus. The number of pixels in the green area was calculated as 5195. g,h) a 59-year-old male patient presented with axial CT images passing through the level of the esophageal hiatus. The number of pixels in the green area was calculated as 640
CT: Computerized tomography

Statistical Analysis

The analysis was performed using the Statistical Package for the Social Sciences International Business Machines version 20 (SPSS Inc., Chicago, IL, USA). The relationship between variables was evaluated using the Pearson correlation, and independent groups were investigated by the Chi-square and Mann-Whitney U tests. The receiver operating characteristic curve was created to quantitatively measure data, and cut-off values were calculated according to sensitivity and specificity values. P-values of<0.05 were considered statistically significant.

RESULTS

Participants

This study included 24 male and 22 female patients with a mean age of 46 years (range, 23-74).

Correlation Between EGD and CT Imaging

Participants were classified into two groups based on EGD results as HH and hiatal insufficiency. The hiatal insufficiency group included 26 patients, whereas 20 in the HH group. The CT images evaluation determined 4 patients in the possible hernia group, 19 in the probable hernia group, and 23 in the definite hernia group (Table 1). A statistically significant correlation was found between the groups using the Pearson correlation test (p<0.05). The Chi-square tests were used to evaluate the difference between the groups, which revealed a statistically significant difference (p=0.001).

DeMeester Score and CT Measurements

DeMeester scores of 14 patients were <14.72, whereas scores of 32 patients were >14.72. The CT images evaluation determined 4 patients in the possible hernia group, 19 in the probable hernia group, and 23 in the definite hernia group. The Chi-square test was used to analyze the differences between groups, which revealed no statistically significant difference (p=0.17). No statistically significant difference was observed between the number of hiatal area pixels and DeMeester scores using the Mann-Whitney U test (p=0.49) (Table 2). When the cut-off value for the number of hiatal area pixels was set as 600, the sensitivity and specificity of CT imaging for correlation with DeMeester score were 50% and 48%, respectively (Figure 3). CT imaging of 5 patients was unable to measure the angle of His because of severe sliding HH. The mean degree of angle was 90.8° in patients who had <14.7 DeMeester scores, whereas 94.2° in patients who had >14.7 DeMeester scores. No statistically significant difference was found between the angle of His and DeMeester scores using the Mann-Whitney U test (p=0.45). The sensitivity and specificity of CT imaging for the DeMeester score were 48% and 50%, respectively when the cut-off value for the angle of His was set as 92.1° (Figure 3).

Table 1. Evaluation of EGD and CT results

EGD	Possible	Probable	Definite	Total
Hiatal insufficiency	4	15	7	26
Hiatal hernia	0	4	16	20
Total	4	19	23	46

EGD: Esophagogastroduodenoscopy, CT: Computerized tomography

Table 2. Evaluation of DeMeester score and number of pixels and angel of His

DeMeester score	Number of pixels (mean)	Angel of His (mean)
<14.7	636	90.8°
>14.7	1085	94.2°
p	0.49	0.45

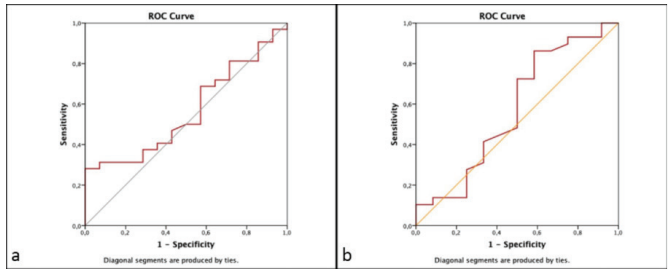

Figure 3. a) Receiver operating characteristic analysis of the number of hiatal area pixels for correlation with DeMeester score. b) Receiver operating characteristic analysis of the angle of His for correlation with DeMeester score

ROC: Receiver operating characteristic

DISCUSSION

Anatomical changes of the esophageal hiatus are important for surgeons before anti-reflux or HH surgery (14). The surgeon's decision about hernia repair method depends on HH size (15). EGD provides diagnosis and description of mucosal abnormalities that are associated with reflux and HH or reflux complications. PH-metry is used to show the presence of reflux in cases with positive EGD results in the preoperative management. This study evaluated the CT imaging measurements of the esophageal hiatus and EGD results with DeMeester scores in patients with GERD-like symptoms to show the effectiveness of CT imaging as a replacement of pH-metry, an uncomfortable method in the esophagus for 24 hours.

First, our study provides CT imaging to assess HH in patients with GERD-like symptoms. CT imaging shows a well diagnostic capacity for HH diagnosis compared with EGD results. None of the patients with EGD result in the HH group was included in the possible group (hernia length 0-1 cm) in CT examination, whereas 16 patients were included in the definite group (hernia length >2 cm) and 4 in the probable group (hernia length 1-2 cm). Radiological methods and HH presence is an old area of research. Koch et al. (11) investigated the association between HH size that was measured in the preoperative period and the esophageal hiatus size in the intraoperative period. They used barium swallow examination and demonstrated no correlation between the preoperative and postoperative measurements (p=0.073). CT examination was more successful in anatomical details, thus studies were started to publish with this imaging method. Revelli et al. (16) published a study in 2015, which revealed that it is not necessary to report minimally sliding HH when reporting CT with water enema and CT colonography examinations especially in patients with non-GERD-related symptoms. All patients in our study had GERD-related symptoms. Unlike our study, a healthy control group was included in their study and CT techniques were performed by increasing the intestinal content and abdominal distention. They emphasized that the patient's anamnesis and symptoms were very important in evaluating CT sections. Another study by Ouyang et al. (12) revealed the presence of HH that correlated with large hiatus and GERD with multiplanar CT imaging. Additionally, the presence of HH was not correlated with endoscopic findings, as in our study. One study showed that endoscopic gastroesophageal flap valve (GEFV) grade has a good correlation with HH presence in CT imaging (17).

Second, correlations between DeMeester score and anatomical CT measurements of the esophageal hiatus were not statistically significant. Possible, probable, and definite HH groups had no statistically significant score differences. However, the study published by Ouyang et al. (12) revealed that patients with HH had more GERD. This difference may be related to the method used to detect GERD. They considered as positive those patients who had heartburn and typically used medication to treat GERD. All patients had heartburn and were treated with typical medication for 6 months. PH-metry was used, which is accepted as the gold standard for GERD diagnosis (18,19). Secondly, the number of participants who had a DeMeester score of <4.7 was only 14, whereas 32 in the DeMeester score of >14.7. A feasibility study researched the efficacy of 320-row area detector CT to assess morphological abnormalities of the esophageal hiatus (20). Their study participants were volunteers in good health and patients diagnosed with esophagitis caused by reflux. They found more occurrence of HH in patients with severe RE, which is explained by the dynamic-like technique in CT examination (non-swallowing and swallowing phases) and different patient profiles. Another parameter that was measured as the number of hiatal area pixels. Similarly, we found no statistically significant differences between the two groups according to the DeMeester score. Additionally, low sensitivity and specificity (50% and 48%, respectively) values were obtained with a cut-off value of 600 for the number of pixels. Many studies investigated the hiatal area in the literature, but none directly investigated the DeMeester score and the number of hiatal area pixels (12,17,20). The study published by Ouyang et al. (12) showed that patients with GERD had larger hiatuses than the normal (healthy volunteers) group. As previously mentioned, this difference may be related to the method used to detect GERD. However, their measurement technique was not significantly different from ours. They made CT postprocessing in a double-oblique plane to demonstrate the hiatal area and manually trace the hiatus then calculate this area in mm^2. We checked the sagittal and coronal reformatted planes before measurement and manually traced the correct section and calculated the number of hiatal area pixels. The study results published by Jeon et al. (17) revealed abnormal GEFV associated with larger diaphragmatic hiatus. Unlike our study, they compared the GEFV to the hiatal area, whereas we compared the presence of reflux and the hiatal area. Fukazawa et al. (20) showed that patients with RE showed larger hiatal area and greater His angle than healthy volunteers. They measured the horizontal size of the diaphragmatic hiatus in mm^2. We found no statistically significant differences between the angle of His and two groups according to the DeMeester score. Additionally, very low sensitivity and specificity (50% and 48%, respectively) values were obtained with a cut-off degree of 92.1°. Yildirim et al. (10) found the sensitivity and specificity of ultrasound for reflux diagnosis as 76% and 72%, respectively, when the cut-off value of the angle of His was set as 138.5°. The same study revealed the sensitivity and specificity values as 83% and 80%, respectively, for CT imaging with the same cut-off value (10). This difference in the literature is due to the angle of His variability due to dynamic anatomy. The angle of sensation may differ during and after swallowing or inspiration and expiration. Therefore, dynamic and real-time imaging has been investigated. In 2010 Curcic et al. (21) showed that MRI has a great agreement in reflux diagnosis with the high-resolution manometry as a reference standard.

A recently published study by Seif Amir Hosseini et al. (22) evaluated 91 patients with GERD-like symptoms. Reflux was

detected in 60 of 91 patients (66%) by real-time MRI. The pH-metry results revealed reflux in 41 of 91 patients (45%). Additionally, reflux was detected by impedance in 54 of 91patients (59%). Compared to pH-metry and impedance, real-time MRI sensitivity, specificity, and PPV were 0.78, 0.67, and 0.87, respectively. Real-time MRI was observed as a favorable useful diagnostic method for GERD due to its relation with pH-metry and impedance results and its high positive predictive value. It is a non-invasive method, thus it can be used before other invasive methods.

Study Limitations

Our study had some limitations. First, a small number of patients was included and the method is retrospective. DeMeester score and CT imaging measurement findings were compared in patients with GERD-like symptoms. DeMeester's score is based on acidic reflux; however, basic reflux can also cause symptoms in patients.

CONCLUSION

The relationship between anatomical data obtained from CT imaging and pH-metry is unclear due to differently designed studies in the literature. However, anatomical details of esophageal hiatus are correlated with endoscopy findings in CT imaging. MR examination should be used in future studies due to its dynamic and real-time sequences.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to all patients who participated in this study.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (no: 15916306-604.01.01).

Informed Consent: All patients signed written informed consent before every medical examination.

Authorship Contributions

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

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. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54:710-7.
2. Manning MA, Shafa S, Mehrotra AK, Grenier RE, Levy AD. Role of Multimodality Imaging in Gastroesophageal Reflux Disease and Its Complications, with Clinical and Pathologic Correlation. Radiographics 2020;40:44-71.
3. Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, et al. American Gastroenterological Association Medical Position Statement on the Management of Gastroesophageal Reflux Disease. Gastroenterology 2008;135:1383-91.
4. Johnston BT, Troshinsky MB, Castell JA, Castell DO. Comparison of barium radiology with esophageal pH monitoring in the diagnosis of gastroesophageal reflux disease. Am J Gastroenterol 1996;91:1181-5.
5. Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut 2018;67:1351-62.
6. Saleh CM, Smout AJ, Bredenoord AJ. The diagnosis of gastro-esophageal reflux disease cannot be made with barium esophagograms. Neurogastroenterol Motil 2015;27:195-200.
7. Kulinna-Cosentini C, Schima W, Cosentini EP. Dynamic MR imaging of the gastroesophageal junction in healthy volunteers during bolus passage. J Magn Reson Imaging 2007;25:749-54.
8. Seif Amir Hosseini A, Beham A, Uhlig J, Streit U, Uhlig A, Ellenrieder V, et al. Intra- and interobserver variability in the diagnosis of GERD by real-time MRI. Eur J Radiol 2018;104:14-9.
9. Lambert L, Grusova G, Burgetova A, Matras P, Lambertova A, Kuchynka P. The predictive value of computed tomography in the detection of reflflux esophagitis in patients undergoing upper endoscopy. Clin Imaging 2018;49:97-100.
10. Yildirim D, Ekçi B, Gürses B, Oruç F. Evaluation of the gastro-oesophageal junction: defining the incompetent cardio-oeosophageal angle non-invasively with ultrasound and computerized tomography. J Int Med Res 2011;39:1193-200.
11. Koch OO, Schurich M, Antoniou SA, Spaun G, Kaindlstorfer A, Pointner R, et al. Predictability of hiatal hernia/defect size:is there a correlation between pre- and intraoperative findings? Hernia 2014;18:883-8.
12. Ouyang W, Dass C, Zhao H, Kim C, Criner G; COPDGene Investigators. Multiplanar MDCT measurement of esophageal hiatus surface area: association with hiatal hernia and GERD. Surg Endosc 2016;30:2465-72.
13. DeMeester TR, Wang CI, Wernly JA, Pellegrini CA, Little AG, Klementschitsch P, et al. Technique, indications, and clinical use of 24-hour esophageal pH monitoring. J Thorac Cardiovasc Surg 1980;79:656-70.
14. Kahrilas PJ, Kim HC, Pandolfino JE. Approaches to the diagnosis and grading of hiatal hernia. Best Pract Res Clin Gastroenterol 2008;22:601-16.
15. Grubnik VV, Malynovskyy AV. Laparoscopic repair of hiatal hernias: new classification supported by long-term results. Surg Endosc 2013;27:4337-46.
16. Revelli M, Furnari M, Bacigalupo L, Paparo F, Astengo D, Savarino E, et al. Incidental physiological sliding hiatal hernia: a single center comparison study between CT with water enema and CT colonography. Radiol Med 2015;120:683-9.
17. Jeon HK, Kim GH, Lee NK, Kim S, Lee BE, Song GA. Analysis of computed tomographic findings according to gastroesophageal flap valve grade. Korean J Intern Med 2018;33:295-303.

18. Fink SM, McCallum RW. The Role of Prolonged Esophageal pH Monitoring in the Diagnosis of Gastroesophageal Reflux. JAMA 1984;252:1160-4.
19. DeMeester T, Wang C-I, Johnson L, Skinner D. Comparison of Clinical-Test for Detection of Gastroesophageal Reflux. Basel, Switzerland: Karger Allschwilerstrasse 10, Ch-4009;1979.
20. Fukazawa K, Furuta K, Adachi K, Shimura S, Kamiyama K, Aimi M, et al. Continuous imaging of esophagogastric junction in patients with reflux esophagitis using 320-row area detector CT: a feasibility study. J Gastroenterol Hepatol 2013;28:1600-7.
21. Curcic J, Fox M, Kaufman E, Forras-Kaufman Z, Hebbard GS, Roy S, et al. Gastroesophageal junction: structure and function as assessed by using MR imaging. Radiology 2010;257:115-24.
22. Seif Amir Hosseini A, Uhlig J, Streit U, Gliem N, Wedi E, Ellenrieder V, et al. Real-time MRI for dynamic assessment of gastroesophageal reflux disease: Comparison to pH-metry and impedance. Eur J Radiol 2020;125:108856.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:334-342
DOI: 10.4274/BMJ.galenos.2021.78790

Research

The Relationship Between Prognostic and Organ Failure Scoring Systems Such as APACHE II, SAPS II, MODS, SOFA and GCS and Quantitative Amino Acid Levels in Intensive Care Unit Patients

Yoğun Bakım Ünitesindeki Hastalarda APACHE II, SAPS II, MODS, SOFA ve GKS gibi Prognostik ve Organ Yetmezliği Skorlama Sistemleri ile Serum Amino Asit Düzeyleri Arasındaki İlişki

Sema Uçak Basat[1], Rıdvan Sivritepe[2], Okcan Basat[3], Arzu Baygül[4], Aydın Duygu[5], Pınar Eker[6], Kamil Özdil[7]

[1]University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Internal Medicine, Istanbul, Turkey
[2]Istanbul Medipol University Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey
[3]University of Health Sciences Turkey, Gaziosmanpaşa Taksim Training and Research Hospital, Clinic of Family Medicine, Istanbul, Turkey
[4]Koç University Faculty of Medicine, Department of Biostatistics, Istanbul, Turkey
[5]Amino Acid Science Ltd, Translation and Innovation Hub, London
[6]Maltepe University Faculty of Medicine, Laboratory Director, Istanbul, Turkey
[7]University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Gastroenterology, Istanbul, Turkey

ABSTRACT

Objective: This study aimed to investigate the relationship between the prognostic and organ failure scoring systems and quantitative amino acid levels in patients in the intensive care unit (ICU).

Methods: A total of 45 patients over 45 years old, who were admitted to the ICU, were included in the study. Physical examinations of all patients were performed, and blood tests (including serum amino acids) were analyzed. Sequential organ failure assessment (SOFA), multiple organ dysfunction score (MODS), simplified acute physiology score II (SAPS II), acute physiology and chronic health evaluation II (APACHE II), and glasgow coma scale (GCS) scores of patients were calculated. Risk ratios were determined according to the mortality and organ failure scores of patients, and patients were grouped as high-risk and low risk. All these parameters were compared between these groups, and the relationship between amino acid levels and risk scores was evaluated. Statistical significance level was determined as a p-value of <0.05.

Results: This study was carried out on 45 patients, 23 females and 22 males. The mean age of the patients was 74±11 years. In high-risk patients compared to low-risk group; methionine, ornithine, and phenylalanine levels according to APACHE II; beta-alanine, cystine, 3-methyl histidine, phenylalanine, and proline levels according to SAPS II; alanine, beta-alanine, phenylalanine, glycine, histidine, methionine, and ornithine levels according to GCS were significant different (p<0.05 for all). We found a significant positive correlation between the APACHE II score and beta alanine (r=0.466; p=0.001), citrulline (r=0.394; p=0.007), ethanolamine (r=0.366; p=0.013), histidine (r=0.353; p=0.017), 3-methyl histidine (r=0.450; p=0.002), ornithine (r=0.445; p=0.002), phenylalanine (r=0.548; p<0.001). There was a significant positive correlation between the SAPS II score and beta alanine (r=0.403; p=0.006), cystathionine (r=0.341; p=0.022), ethanolamine (r=0.356; p=0.017), 3-methyl histidine (r=0.402; p=0.006), ornithine (r=0.349; p=0.019), phenylalanine (r=0.525; p<0.001) and between the MODS score and alanine (r=0.340; p=0.022), beta alanine (r=0.407; p=0.006), cystathionine (r=0.352; p=0.018), ethanolamine (r=0.358; p=0.0169), histidine (r=0.495; p=0.001), 3-methyl histidine (r=0.407; p=0.006), methionine (r=0.462; p=0.001), ornithine (r=0.360; p=0.015), phenylalanine (r=0.621; p<0.001), proline (r=0.445; p=0.002). We found a significant positive correlation between the SOFA score and alanine (r=0.547; p<0.0019), beta-alanine (r=0.354; p=0.0179), arginine (r=0.423; p=0.004), cystathionine (r=0.423; p=0.004), ethanolamine (r=0.437; p=0.003), glycine (r=0.399; p=0.007), histidine (r=0.512; p<0.001), 3-methyl histidine (r=0.327; p=0.028), leucine (r=0.376; p=0.011), methionine (r=0.585; p<0.001), ornithine (r=0.467; p=0.001), phenylalanine

Address for Correspondence: Rıdvan Sivritepe, Istanbul Medipol University Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey
Phone: +905452605957 E-mail: dr.ridvansivritepe@gmail.com ORCID ID: orcid.org/0000-0003-0547-1883

Cite as: Uçak Basat S, Sivritepe R, Basat O, Baygül A, Duygu A, Eker P, Özdil K. The Relationship Between Prognostic and Organ Failure Scoring Systems Such as APACHE II, SAPS II, MODS, SOFA and GCS and Quantitative Amino Acid Levels in Intensive Care Unit Patients. Med J Bakirkoy 2021;17:334-342

Received: 16.07.2021
Accepted: 01.10.2021

(r=0.644; p<0.001), proline (r=0.523; p<0.001), threonine (r=0.371; p=0.012). Also, there was a significant negative correlation between GCS score and beta alanine (r=-0.390; p=0.008), ethanolamine (r=-0.364; p=0.014), glycine (r=-0.360; p=0.015), ornithine (r=-0.510; p=0.000), phenylalanine (r=-0.433; p=0.003).

Conclusion: This study found significantly higher methionine, ornithine, phenylalanine, beta-alanine, cystine, 3-methyl histidine, proline, alanine, glycine, and histidine levels in patients with high-risk scores.

Keywords: Amino acids, intensive care units, prognosis, risk factors, APACHE, simplified acute physiology score, organ dysfunction scores

ÖZ

Amaç: Bu çalışmada yoğun bakım ünitesindeki (YBÜ) hastalarda prognostik ve organ yetmezliği skorlama sistemleri ile serum aminoasit düzeyleri arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Çalışmaya 45 yaş üstü herhangi bir nedenden dolayı dahiliye YBÜ'ye interne edilen 45 hasta dahil edildi. Tüm hastaların fizik muayeneleri yapıldı ve kan tetkikleri (kantitatif amino asitler dahil) analiz edildi. Hastaların sıralı organ yetmezliği değerlendirmesi (SOFA), çoklu organ disfonksiyon skoru (MODS), Basitleştirilmiş akut fizyoloji skoru II (SAPS II), akut fizyoloji ve kronik sağlık değerlendirmesi II (APACHE II), ve glasgow koma skalası (GCS) skorları hesaplandı. Kantitatif aminoasit düzeyleri ölçüldü. Hastaların mortalite ve organ yetmezliği skorlarına göre risk oranları belirlendi ve hastalar yüksek riskli ve düşük riskli olarak gruplandırıldı. Tüm parametreler bu gruplar arasında karşılaştırıldı ve amino asit seviyeleri ile risk skorları arasındaki ilişki değerlendirildi. İstatistiksel analizde p<0,05 kabul edildi.

Bulgular: Bu çalışma 23'ü kadın, 22'si erkek 45 hasta üzerinde gerçekleştirildi. Hastaların ortalama yaşı 74±11 yıl idi. Hastalar APACHE II skoruna göre düşük riskli (<25 puan) ve yüksek riskli (≥25 puan) diye iki gruba ayrıldığında metiyonin (p=0,011), ornitin (p=0,019) ve fenilalanin (p<0,001); SAPS II skoruna göre düşük riskli (≤40 puan) ve yüksek riskli (>40 puan) diye iki gruba ayrıldığında beta-alanin (p=0,038), sistin (p=0,038), 3-metil histidin (p=0,024), fenilalanin (p=0,011) ve prolin (p=0,027); GKS skoruna göre yüksek riskli (≤8 puan), orta riskli (8-13 puan) ve düşük riskli (≥13 puan) diye üç gruba ayrıldığında alanin (p=0,031), beta-alanin (p=0,035), fenilalanin (p=0,006), glisin (p=0,005), histidin (p=0,007), metiyonin (p=0,044) ve ornitin (p=0,007) düzeyleri arasında anlamlı farklılık saptandı. APACHE II skoru ile beta alanin (r=0,466; p=0,001), sitrulin (r=0,394; p=0,007), etanolamin (r=0,366; p=0,013), histidin (r=0,353; p=0,017), 3-metil histidin (r=0,450; p=0,002), ornitin (r=0,445; p=0,002), fenilalanin (r=0,548; p<0,001) arasında pozitif yönlü orta düzeyde; SAPS II skoru ile beta alanin (r=0,403; p=0,006), sistatyonin (r=0,341; p=0,022), etanolamin (r=0,356; p=0,017), 3-metil histidin (r=0,402; p=0,006), ornitin (r=0,349; p=0,019), fenilalanin (r=0,525; p<0,001) arasında pozitif yönlü orta düzeyde, glisin, valin arasında pozitif yönlü zayıf düzeyde; MODS skoru ile alanin (r=0,340; p=0,022), beta alanin (r=0,407; p=0,006), sistatyonin (r=0,352; p=0,018), etanolamin (r=0,358; p=0,0169), histidin (r=0.495; p=0,001), 3-metil histidin (r=0,407; p=0,006), metiyonin (r=0,462; p=0,001), ornitin (r=0,360; p=0,015), fenilalanin (r=0,621; p<0,001), prolin (r=0,445; p=0,002) arasında pozitif yönlü orta düzeyde; SOFA skoru ile alanin (r=0,547; p<0,0019), beta-alanin (r=0,354; p=0,0179), arginin (r=0,423; p=0,004), sistatyonin (r=0,423; p=0,004), etanolamin (r=0,437; p=0,003), glisin (r=0,399; p=0,007), histidin (r=0,512; p<0,001), 3-metil histidin (r=0,327; p=0,028), lösin (r=0,376; p=0,011), metyonin (r=0,585; p<0,001), ornitin (r=0,467; p=0,001), fenilalanin (r=0,644; p<0,001), prolin (r=0,523; p<0,001), treonin (r=0,371; p=0,012) arasında pozitif yönlü orta düzeyde, GKS skoru ile beta alanin (r=-0,390; p=0,008), etanolamin (r=-0,364; p=0,014), glisin (r=-0,360; p=0,015), ornitin (r=-0,510; p=0,000), fenilalanin (r=-0,433; p=0,003) arasında negatif yönlü orta düzeyde anlamlı korelasyon saptadık.

Sonuç: Bu çalışmada risk skoru yüksek ve prognozu kötü olan hastalarda metiyonin, ornitin, fenilalanin, beta-alanin, sistin, 3-metil histidin, prolin, alanin, glisin, histidin düzeylerinin yüksek olduğunu saptadık. Sonuçlarımız, kritik hastalarda bozulmuş enerji metabolizması ile kas proteini yıkımı arasında yakın ve anlamlı bir ilişki olduğunu düşündürtmektedir.

Anahtar Kelimeler: Amino asitler, yoğun bakım üniteleri, prognoz, risk faktörleri, APACHE, basitleştirilmiş akut fizyoloji skoru, organ disfonksiyon skorları

INTRODUCTION

The metabolic conditions of critical illnesses in the intensive care units (ICU) are quite complex (1). These unitary patients have an increased catabolic state, resting energy expenditure, and metabolic activity, thus these patients should be considered as a privileged group (2,3). This pathological process involved many mechanisms, which result in muscle degeneration and impaired immune response if not treated immediately may delay recovery and cause increased mortality. Therefore, detecting these metabolic disorders is important in the clinical management of these patients. The simplified acute physiology score II (SAPS II), acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA), multiple organ dysfunction score (MODS), and glasgow coma scale (GCS) scoring systems are used to determine the prognosis and disease severity in these patients (4).

The plasma levels of most amino acids are thought to be altered in conditions such as sepsis (5). Therefore, information about the important amino acid levels in patients who are critically ill and the therapeutic approach and its timing is insufficient. This present study aimed to investigate the relationship between prognostic scoring systems, such as SAPS II, APACHE II, MODS, SOFA, and GKS and quantitative amino acid levels, which were used in many scientific fields in recent years.

METHODS

This study was designed as a cross-sectional study and was approved by the local Ethics Committee of University Of Health Sciences Turkey, Ümraniye Training and Research Hospital (date: 17.01.2018; number: B.10.1.TKH.4.34.H.GP.0.01/7) and was conducted following the principles of the Declaration of Helsinki. Written

informed consent was obtained from all participants/relatives. As a result of power analysis, 45 patients were included in the study.

Patients over 45 years of age, who were admitted to our general ICU, did not receive parenteral nutrition support in the first 24 h of admission, had normal liver and kidney functions, and without additional diagnoses of chronic disease were included in the study, regardless of gender. Patients under 45 years old, receiving parenteral nutrition support in the first 24 h of intensive care admission, with diabetes mellitus, chronic liver and kidney failure, chronic infection, neutropenia (≤500 neutrophils/mm^3), and a history of malignancy were excluded from the study. A detailed medical history was taken from all patients and their relatives, and their physical examinations were performed. Biochemical blood tests, hemogram, arterial blood gas, and serum amino acid levels were analyzed. Blood sampling was performed between 08:00 and 10:00 h and taken within the first 48 h of intensive care admission. SOFA, MODS, SAPS II, APACHE II, and GCS scores of patients were calculated.

Metabolic Parameters

Plasma glucose was measured by the enzymatic test method; albumin, aspartate transaminase, and alanine transaminase by enzymatic colorimetric test (Hitachi 747 auto analyzer, German); C-reactive protein by immunoassay; iron-binding capacity, iron, total protein, blood urea nitrogen, and uric acid by spectrophotometer; creatinine by Jaffe' method; bilirubins by diazo method; sedimentation by the Westergren standard method; ferritin by immunechemiluminescence; sodium, and potassium level with ion-selective electrode analysis using Architect plus device. Hemogram parameters were measured by the electrical impedance method using the Mindray BC 6800 device. Blood gas measurements were measured using the ABL800 FLEX device.

Evaluation of Serum Amino Acid Levels

Serum amino acids (alanine, beta-alanine, alpha aminoadipic acid, alpha aminobutyric acid, gamma-aminobutyric acid, arginine, asparagine, aspartic acid, citrulline, cystathionine, Sistine, homocysteine, ethanolamine, glutamine, glutamic acid, glycine, histidine, 1-methyl histidine, 3-methyl histidine, leucine, isoleucine, lysine, hydroxylysine, methionine, ornithine, phenylalanine, proline, hydroxyproline, serine, taurine, threonine, tryptophan, tyrosine, and valine) were separated by liquid chromatography technique using the Shimadzu Prominence UFLC system. The AB Sciex QTRAP 5500 tandem mass spectrometer was used for measurements. The separation of amino acids was carried out at a temperature of 50 °C. The amino acid was determined in plasma using the ARCHITECT i2000SR immunoassay analyzer, Abbott Diagnostics, Abbot Park device.

Calculation of Risk Scores

The patients' APACHE II, MODS, SOFA, and SAPS II scores were calculated using a calculator with parameters such as heart rate, mean arterial pressure, respiratory rate, rectal temperature level, PaO_2/Fio_2, arterial pH, bicarbonate level, sodium level, potassium level, serum creatinine level, hematocrit, leukocyte count, hypotension status, bilirubin level, platelet count, type of hospital admission, presence of chronic disease, age, serum creatinine/blood urea nitrogen ratio, systolic blood pressure, hourly urine output, and GCS score (6-9). The GCS was calculated using the eye-opening, motor, and verbal responses (10). Patients were grouped according to the APACHE II risk score as <25 points: Low risk and ≥25 points: High-risk; the SAPS II score as <41 points: Low risk and ≥4: High-risk; the MODS score as <13 points: Low risk and ≥13 points: High-risk; the SOFA score as <13 points: low risk and ≥13 points: High-risk; and the GCS score as <8 points: high-risk, 8-13 points: medium risk, and >13 low risks.

Statistical Analysis

Continuous variables were described using the mean, standard deviation, minimum, maximum, and median. Spearman's rho coefficient (for two non-normally distributed continuous variables) and Pearson's correlation coefficient (for two normally distributed continuous variables) were used in the correlation analyses. The comparison of continuous variables belonging to more than two groups that did not fit the normal distribution was made with the Kruskal-Wallis test. The Mann-Whitney U test (for two independent and normally distributed variables) and Student's t-test (two independent and normally distributed continuous variables) was used for comparison between groups. Sensitivity and specificity calculations were made to examine the strength of the applied diagnostic tests. Statistical significance was accepted as a p-value of 0.05. MedCalc Statistics program 12.7.7 was used for statistical analysis (MedCalc Software bvba, Ostend, Belgium; http=//www.medcalc.org; 2013).

RESULTS

This study was carried out on 45 patients, wherein 23 were females and 22 were males. The mean age of the patients was 74±11 years and the mean length of ICU stay was 18±18 days. ICU discharge was recorded in 62.2% of the patients, whereas 37.8% died. The risk scores and quantitative amino acid levels of patients are summarized in Table 1.

Table 1. The risk scores and quantitative amino acid levels of the patients (n=45)

	Average	SD	Median	Min	Max
APACHE II	19	8	20	4	35
SAPS II	51	16	50	21	94
MODS	6	3	5	1	18
SOFA	6	3	6	0	15
GCS	10	5	10	3	18
Alanin (µmol/L)	301,54	171,26	245,07	112	924,8
Beta alanin (µmol/L)	1.6	0,9	1.2	1	5.7
Alpha aminoadipic acid (µmol/L)	2,864	2,744	1	1	10.2
Alpha aminobutyric acid (µmol/L)	18.46	13.92	14.3	5.3	71.2
Gama aminobutyric acid (µmol/L)	129	114	110	10	620
Arginine (µmol/L)	50.52	36.78	40	9	192,63
Asparagin (µmol/L)	36.62	15.84	37.72	13.2	89
Aspartic acid (µmol/L)	8,472	6,666	7.1	1.2	37.92
Citruline (µmol/L)	25,336	12,797	24.8	3,198	52
Cystathionine (µmol/L)	14,117	34.88	3.1	0.27	198,96
Sistine (µmol/L)	24,156	11,102	23.72	6.19	56.46
Homocystine (µmol/L)	1,926	2,263	1	0	10.52
Ethanolamine (µmol/L)	10,096	8,839	6	2	35.4
Glutamine (µmol/L)	440,09	157,42	410,6	237	898,61
Glutamic acid (µmol/L)	70.36	32.63	62	26.02	163,78
Glycine (µmol/L)	207,29	114,25	179,5	20.3	619
Histidine (µmol/L)	70.59	24.29	65.5	40	128
1-Methyl histidine (µmol/L)	8,253	11,873	4,516	0.1	63.19
3-Methyl histidine (µmol/L)	16,405	11,032	13.44	0.61	44.5
Leucine (µmol/L)	115,16	43.22	102,7	30	227,39
Isolocine (µmol/L)	69.25	31.3	64	15	171,47
Lysine (µmol/L)	171,18	47.47	165	83	289,36
Hydroxylyzine (µmol/L)	4,879	7,255	1.06	0.23	28.51
Methionine (µmol/L)	29.35	16.83	23.8	8.9	81.06
Ornithine (µmol/L)	107,11	43.59	95.25	39	241
Fenilalanine (µmol/L)	109,51	56.87	96	40	372
Proline (µmol/L)	208,69	86.76	178,23	84	538
Hydroxyproline (µmol/L)	13,219	11,353	9.215	1.45	44.79
Serine (µmol/L)	100,83	48.07	91.09	47	316,64
Taurine (µmol/L)	59.06	58.13	33	6	313,76
Threonine (µmol/L)	122,04	50.29	110	54	259,2
Triptophan (µmol/L)	35.81	18,811	32	6,639	106,4
Tyrosin (µmol/L)	56.85	1852	53.66	14	94.11
Valine (µmol/L)	264,93	359,23	203.2	66	2.587

SD: Standard deviation, Min: Minimum, Max: Maximum, APACHE II: The acute physiology and chronic health evaluation II, SAPS II: Simplified acute physiology score, MODS: Multiple organ dysfunction score, SOFA: Sequential organ failure assessment, GCS: Glasgow coma scale

The correlation analysis between risk scores and quantitative amino acid levels found that as the risk scores of patients increased, the levels of some amino acids also increased. A moderate positive correlation was found between the APACHE II score and beta-alanine, citrulline, ethanolamine, histidine, 3-methyl histidine, ornithine, and phenylalanine; a weak statistically significant positive correlation between the APACHE II score and cystathionine; a moderate positive correlation between the SAPS II score and beta-alanine, cystathionine, ethanolamine, 3-methyl histidine, ornithine, and phenylalanine; a weak statistically significant correlation between the SAPS II score and glycine, and valine; a moderately positive correlation between the MODS score and alanine, beta-alanine, cystathionine, ethanolamine, histidine, 3-methyl histidine, methionine, ornithine, phenylalanine, and proline; a weak positive correlation between MODS score and arginine and leucine; a moderate positive correlation between SOFA score and alanine, beta-alanine, arginine, cystathionine, ethanolamine, glycine, histidine, 3-methyl histidine, leucine, methionine, ornithine, phenylalanine, proline, and threonine; a weak positive and statistically significant correlation between SOFA score and 3-methyl histidine, lysine, and serine; and a moderately statistically significant negative correlation between the GCS score and beta-alanine, ethanolamine, glycine, ornithine, phenylalanine, and proline (Table 2).

The regression analysis between quantitative amino acid levels and risk scores found that a 1-unit change in citrulline increased the APACHE II score by 0.169 times, a 1-unit change in ethanolamine increased the APACHE II score by 0.193 times, and a 1-unit change in 3-methyl histidine increased the APACHE II score by 0.225 times. However, it could not be interpreted due to the multicollinearity problem between other risk scores and amino acid levels.

Methionine, ornithine, and phenylalanine levels were found to be higher in the high-risk group according to the APACHE II risk score ($p=0.011$, $p=0.019$, and $p<0.001$, respectively). Beta-alanine, cystine, 3-methyl histidine, phenylalanine, and proline levels were significantly higher in the high-risk group according to the SAPS II score ($p=0.038$, $p=0.038$, $p=0.024$, $p=0.011$, $p=0.027$, respectively). In addition, alanine, beta-alanine, phenylalanine, glycine, histidine, methionine, and ornithine levels were higher in the high-risk group than in the low risk group according to the GCS score ($p=0.031$, $p=0.035$, $p=0.006$, $p=0.005$, $p=0.007$ $p=0.044$, and $p=0.007$, respectively). When the patients were divided into high-risk and low risk according to MODS and SOFA scores, comparison could not be made because the sample size in both groups was insufficient.

DISCUSSION

This study revealed a significant correlation between mortality and morbidity risk scores and beta-alanine, methionine, ornithine, phenylalanine, cystine, 3-methyl histidine, proline, alanine, glycine, histidine, and cystathionine levels. Present results suggested a close and significant relationship between impaired energy metabolism and muscle protein breakdown in patients who are critically ill.

Amino acids present in serum are metabolites that are released during protein catabolism. Serum amino acid levels are stable in healthy individuals but may change in catabolic states or metabolic diseases. Plasma amino acid levels decrease in cases of nephrotic syndrome, rheumatoid arthritis, and adrenocortical hyperfunction, but increase in malabsorption, diabetes, chronic kidney and liver failure, and septic shock (11). This study provides a theoretical basis to predict mortality and serum amino acid levels of patients in the ICUs. The comprehensive study of serum amino acid levels and risk scores made this study valuable.

ICUs are areas where critically ill and high-risk patients are followed with invasive and non-invasive methods, life-support functions, and intensive treatment using the latest technology (12). The metabolic disorders of patients in these units are quite complex (13). Catabolic events are higher than anabolic events in these patients due to increased cytokine levels and hyperactivity of some inflammatory mediators (14). Many factors affect the prognosis of patients in these units. The patient's current physiological reserve, type of disease, and treatment response are the most important factors. The clinical status of patients in the ICU can instantaneously change, thus their vital activities are mostly supported by external devices and drugs, and their lives continue with high-level treatment and care practice. Prognostic mortality and morbidity calculations related to organ failure are extremely important in this patient group (15). These scores, which are used to determine the severity of the disease, are widely used in the ICUs to measure the degree of organ dysfunction, determine the severity of the disease, and predict the treatment response (15).

Amino acid levels, which are the building blocks of proteins, change in critical diseases (16). Sepsis is an important catabolic process that causes a peripheral energy deficit resulting from the breakdown of muscle proteins, partially increased lean body mass, and increased oxidation of amino acids, primarily, branched-chain amino acids (17). Correlations were shown between the clinical status of critically ill patients, such as sepsis, and certain laboratory

Table 2. Analysis of correlation between risk scores and quantitative amino acids

		APACHE II	SAPS II	MODS	SOFA	GCS
Alanine (µmol/L)	**r**	0.248	0.275	**0.34****	**0.547****	-0.267
	p	0.1	0.067	**0.022**	**<0.001**	0.077
Beta-alanine (µmol/L)	**r**	**0.466****	**0.403****	**0.407****	**0.354****	**-0.39****
	p	**0.001**	**0.006**	**0.006**	**0.017**	**0.008**
Alpha aminoadipic acid (µmol/L)	**r**	0.074	-0.058	0.134	0.179	-0.033
	p	0.627	0.705	0.381	0.24	0.83
Alpha aminobutyric acid (µmol/L)	**r**	0.077	0.017	0.162	0.231	-0.072
	p	0.613	0.914	0.288	0.126	0.638
Gamma-aminobutyric acid (µmol/L)	**r**	0.196	0.152	0.047	0.063	-0.154
	p	0.198	0.318	0.762	0.681	0.312
Arginine (µmol/L)	**r**	0.103	0.089	**0.297****	**0.423****	-0.004
	p	0.499	0.563	**0.047**	**0.004**	0.98
Asparagine (µmol/L)	**r**	0.032	-0.074	-0.169	-0.055	0.154
	p	0.834	0.629	0.268	0.722	0.312
Aspartic acid (µmol/L)	**r**	0.072	-0.182	0.047	0.104	0.08
	p	0.638	0.232	0.761	0.498	0.603
Citrulline (µmol/L)	**r**	**0.394***	0.152*	0.219	0.220*	-0.2
	p	**0.007**	0.319	0.148	0.147	0.189
Cystathionine (µmol/L)	**r**	**0.315****	**0.341****	**0.352****	**0.423****	-0.227
	p	**0.035**	**0.022**	**0.018**	**0.004**	0.134
Sistine (µmol/L)	**r**	0.216*	0.110*	0.182	0.124*	0.026
	p	0.154	0.473	0.233	0.415	0.867
Homocysteine (µmol/L)	**r**	-0.013	-0.093	-0.2	-0.087	0.107
	p	0.934	0.542	0.188	0.571	0.484
Ethanolamine (µmol/L)	**r**	**0.366****	**0.356****	**0.358****	**0.437****	**-0.364****
	p	**0.013**	**0.017**	**0.016**	**0.003**	**0.014**
Glutamine (µmol/L)	**r**	0.184	0.045	0.076	0.216	-0.078
	p	0.227	0.768	0.621	0.153	0.613
Glutamic acid (µmol/L)	**r**	0.235	0.208	0.064	0.027	-0.194
	p	0.121	0.171	0.674	0.859	0.201
Glycine (µmol/L)	**r**	0.187	**0.339****	0.207	**0.399****	**-0.36****
	p	0.218	**0.023**	0.172	**0.007**	**0.015**
Histidine (µmol/L)	**r**	**0.353****	0.255	**0.495****	**0.512****	-0.282
	p	**0.017**	0.091	**0.001**	**<0.001**	0.061
1-Methyl histidine (µmol/L)	**r**	-0.169	-0.146	-0.05	-0.091	0.058
	p	0.268	0.34	0.745	0.554	0.703
3-Methyl histidine (µmol/L)	**r**	**0.45****	**0.402****	**0.407****	**0.327****	-0.232
	p	**0.002**	**0.006**	**0.006**	**0.028**	0.126
Leucine (µmol/L)	**r**	0.200*	0.120*	**0.33****	**0.376***	-0.171
	p	0.187	0.433	**0.027**	**0.011**	0.26
Isoleucine (µmol/L)	**r**	0.118*	0.011*	0.225	0.303*	0.015
	p	0.464	0.947	0.158	0.054	0.927
Lysine (µmol/L)	**r**	0.149	0.095	0.204	**0.336****	-0.085
	p	0.329	0.534	0.178	**0.024**	0.579

Table 2. Contunued						
Hydroxylysine (µmol/L)	**r**	0.16	0.051	0.2	0.252	-0.093
	p	0.293	0.738	0.188	0.095	0.542
Methionine (µmol/L)	**r**	0.27	0.268	**0.462****	**0.585****	-0.263
	p	0.073	0.075	**0.001**	**<0.001**	0.081
Ornithine (µmol/L)	**r**	**0.445****	**0.349****	**0.36****	**0.467****	**-0.51****
	p	**0.002**	**0.019**	**0.015**	**0.001**	**0**
Phenylalanine (µmol/L)	**r**	**0.548****	**0.525****	**0.621****	**0.644****	**-0.433****
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.003**
Proline (µmol/L)	**r**	0.283	0.277	**0.445****	**0.523****	-0.25
	p	0.06	0.065	**0.002**	**<0.001**	0.097
Hydroxyproline (µmol/L)	**r**	-0.135	-0.092	-0.227	0.042	0.191
	p	0.376	0.547	0.133	0.784	0.209
Serine (µmol/L)	**r**	-0.085	-0.088	0.06	**0.335****	-0.003
	p	0.581	0.565	0.697	**0.025**	0.984
Taurine (µmol/L)	**r**	0.241	0.079	0.174	0.074	-0.066
	p	0.111	0.608	0.253	0.629	0.668
Threonine (µmol/L)	**r**	-0.005	0.004	0.118	**0.371****	-0.058
	p	0.972	0.979	0.44	**0.012**	0.703
Tryptophan (µmol/L)	**r**	0.018	0.101	0.179	0.257	-0.153
	p	0.905	0.51	0.239	0.088	0.317
Tyrosin (µmol/L)	**r**	-0.035*	0.066*	-0.079	0.115*	0.051
	p	0.818	0.665	0.607	0.451	0.741
Valine (µmol/L)	**r**	0.119*	**0.319***	0.278	0.228*	-0.154
	p	0.435	**0.033**	0.065	0.133	0.314

**Spearman's rho p, *Pearson p APACHE II: The acute physiology and chronic health evaluation II, SAPS II: Simplified acute physiology score, MODS: Multiple organ dysfunction score, SOFA: Sequential organ failure assessment, GCS: Glasgow coma scale

values (18). However, very few studies showed the relationship between serum amino acid values and disease follow-up. Freund et al. (19) revealed that some amino acid levels can be used as a marker of disease severity and prognosis. Conversely, a study by Vente et al. (5) suggested that amino acid levels show nonspecific trends in critically ill patients, and therefore, may not be useful in predicting disease severity. However, the current study revealed that some amino acids were associated with prognosis.

A study determined that the level of sulfur-containing amino acids, especially taurine, was lower in patients with severe sepsis, and serum taurine level and SOFA and APACHE II scores showed a weak negative correlation (20). However, our study revealed that taurine level was not associated with any risk score. Again, in the same study, sulfur-containing amino acids, such as methionine, cysteine, and cystine, were found to be significantly lower in patients with severe sepsis (20). Our study revealed that cysteine was correlated with APACHE II, SAPS II, MODS, and SOFA, and methionine was correlated with MODS and SOFA scores. In the same study, histidine, citrulline, proline, ornithine, tryptophan, threonine, tyrosine, isoleucine, valine, lysine, asparagine, cystathionine, and leucine levels were found to be lower in patients with sepsis (20). However, our study revealed that these amino acid levels were higher in patients who are critically ill.

Citrulline was shown to improve vascular function, lower blood pressure, and increase peripheral blood flow by increasing nitric oxide synthesis (21). The present study revealed that citrulline levels were not low in patients with high-risk scores. This significant effect is explained by the increased peripheral oxygenation and regulation of the immune system. Low levels of branched-chain amino acids, such as isoleucine, leucine, and valine, were shown to promote protein catabolism and decrease muscle protein synthesis (22). However, our study did not find a significant relationship between these amino acid levels and prognostic risk scores.

A study by Beale et al. (23) found a correlation between sulfur-containing amino acid levels and SOFA score in patients with sepsis and emphasized that the levels of

these amino acids are low in patients with high-risk scores and amino acids- rich diet is important in the nutritional therapy of these patients. However, our study revealed no association between cystine, a sulfur-containing amino acid, and any risk score. A positive correlation was found between methionine, another sulfur-containing amino acid, and MODS and SOFA scores in our study. Another study detected higher levels of alanine and branched-chain amino acids in patients recovering from sepsis (24). However our study found no correlation between the alanine or other branched-chain amino acids and risk scores.

Ornithine is an essential amino acid involved in the urea cycle (25) and is known to positively affect liver functions and help detoxify harmful substances. In addition, ornithine positively affects wound healing and strengthens the immune system (25). Ornithine is metabolized to L-arginine (26). L-arginine stimulates the release of growth hormones from the pituitary. In catabolic conditions, the plasma L-arginine level is affected (27). The present study found that ornithine levels increased in patients who are critically ill with poor prognostic risk scores. This result was in parallel with the data in the literature.

Study Limitations

The present study had some limitations. First, our study was a cross-sectional study. Therefore, a causal relationship could not be established between prognostic and organ failure scoring systems and serum amino acid levels. Second, this study was designed as a single-center study, thus our results may not be valid for all patients admitted to the ICU. Third, serum amino acid analysis and risk score calculations were evaluated at a single time point. Despite all these limitations, to the best of our knowledge, there is no such extensive study on this subject in the literature, thus the present study is valuable.

CONCLUSION

The present study is a guide for the prognosis and clinical treatment of patients who are critically ill in the ICUs. The study found that beta-alanine, ornithine, phenylalanine, ethanolamine, cystathionine, and 3 methyl histidine were correlated with prognostic risk scores in patients who are critically ill. Therefore, we believe that these amino acids can be used as markers to show the prognosis and severity of metabolic disorders of patients in the ICU.

ETHICS

Ethics Committee Approval: This study was designed as a cross-sectional study and was approved by the Local Ethics Committee of University of Health Sciences Turkey, Ümraniye Training and Research Hospital (date: 17.01.2018; number: B.10.1.TKH.4.34.H.GP.0.01/7) and was conducted following the principles of the Declaration of Helsinki.

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

Authorship Contributions

Surgical and Medical Practices: S.U.B., R.S., K.Ö., Concept: S.U.B., R.S., O.B., Design: S.U.B., R.S., A.D., K.Ö., Data Collection or Processing: R.S., P.E., Analysis or Interpretation: A.B., P.E., Literature Search: R.S., A.D., Writing: R.S., O.B., A.B., K.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. Mickiewicz B, Tam P, Jenne CN, Leger C, Wong J, Winston BW, et al. Integration of metabolic and inflammatory mediator profiles as a potential prognostic approach for septic shock in the intensive care unit. Crit Care 2015;19:11.
2. Levy MM, Artigas A, Phillips GS, Rhodes A, Beale R, Osborn T, et al. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study. Lancet Infect Dis 2012;12:919-24.
3. Michie HR. Metabolism of sepsis and multiple organ failure. World J Surg 1996;20:460-4.
4. Rosenberg AL. Recent innovations in intensive care unit risk-prediction models. Curr Opin Crit Care 2002;8:321-30.
5. Vente JP, von Meyenfeldt MF, van Eijk HM, van Berlo CL, Gouma DJ, van der Linden CJ, et al. Plasma-amino acid profiles in sepsis and stress. Ann Surg 1989;209:57-62.
6. APACHE II Score Estimates ICU mortality. MDCalc ©2005-2021 Available from: URL: https://www.mdcalc.com/apache-ii-score.
7. Sequential Organ Failure Assessment (SOFA) Score Predicts ICU mortality based on lab results and clinical data. MDCalc ©2005-2021 Available from: URL:https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score.
8. Multiple Organ Dysfunction Score (MODS) © 2021 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA Available from: https://www.merckmanuals.com/professional/multimedia/clinical-calculator/clinicalcalculator_en_v48814872.
9. Simplified Acute Physiology Score (SAPS) II Estimates mortality in ICU patients, comparable to APACHE II. MDCalc ©2005-2021 Available from: URL:https://www.mdcalc.com/simplified-acute-physiology-score-saps-ii.
10. Rowley G, Fielding K. Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users. Lancet 1991;337:535-8.
11. Bender DA. Amino Acid Metabolism. John Wiley & Sons, The Atrium Southern Gate Chichester West Sussex UK 2 Jul 2012 Availablefrom:https://books.google.com.tr/books?hl=tr&lr=&id=CLok9jcTFVsC&oi=fnd&pg=PT8&dq=Disturbances+of+amino+acid+metabolism&ots=H6VHQTLoIL&sig=

dJ9SikZwKhOUHYhYqdsw0tRKJ_Q&redir_esc=y#v=onepage&q=Disturbances%20of%20amino%20acid% 20metabolism&f =false.

12. Weil MH, Tang W. From intensive care to critical care medicine: a historical perspective. Am J Respir Crit Care Med 2011;183:1451-3.
13. Christopher KB. Nutritional metabolomics in critical illness. Curr Opin Clin Nutr Metab Care 2018;21:121-5.
14. Faix JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci 2013;50:23-36.
15. Fleig V, Brenck F, Wolff M, Weigand MA. Scoring-Systeme in der Intensivmedizin : Grundlagen, Modelle, Anwendung und Grenzen [Scoring systems in intensive care medicine : principles, models, application and limits]. Anaesthesist 2011;60:963-74.
16. Heyland DK, Weijs PJ, Coss-Bu JA, Taylor B, Kristof AS, O'Keefe GE, et al. Protein Delivery in the Intensive Care Unit: Optimal or Suboptimal? Nutr Clin Pract 2017;32(1_suppl):58S-71S.
17. Mira JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, et al. Sepsis Pathophysiology, Chronic Critical Illness, and Persistent Inflammation-Immunosuppression and Catabolism Syndrome. Crit Care Med 2017;45:253-62.
18. Thiel SW, Rosini JM, Shannon W, Doherty JA, Micek ST, Kollef MH. Early prediction of septic shock in hospitalized patients. J Hosp Med 2010;5:19-25.
19. Freund H, Atamian S, Holroyde J, Fischer JE. Plasma amino acids as predictors of the severity and outcome of sepsis. Ann Surg 1979;190:571-6.
20. Su L, Li H, Xie A, Liu D, Rao W, Lan L, et al. Dynamic changes in amino acid concentration profiles in patients with sepsis. PLoS One 20157;10:e0121933.
21. Figueroa A, Wong A, Jaime SJ, Gonzales JU. Influence of L-citrulline and watermelon supplementation on vascular function and exercise performance. Curr Opin Clin Nutr Metab Care 2017;20:92-8.
22. De Bandt JP, Cynober L. Therapeutic use of branched-chain amino acids in burn, trauma, and sepsis. J Nutr 2006;136(1 Suppl):308S-13S.
23. Beale RJ, Sherry T, Lei K, Campbell-Stephen L, McCook J, Smith J, et al. Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. Crit Care Med 2008;36:131-44.
24. Freund HR, Ryan JA Jr, Fischer JE. Amino acid derangements in patients with sepsis: treatment with branched chain amino acid rich infusions. Ann Surg 1978;188:423-30.
25. de Oliveira LF, Navarro BV, Cerruti GV, Elbl P, Minocha R, Minocha SC, et al. Polyamine- and Amino Acid-Related Metabolism: The Roles of Arginine and Ornithine are Associated with the Embryogenic Potential. Plant Cell Physiol 2018;59:1084-98.
26. Tsuei BJ, Bernard AC, Barksdale AR, Rockich AK, Meier CF, Kearney PA. Supplemental enteral arginine is metabolized to ornithine in injured patients. J Surg Res 2005;123:17-24.
27. Kurauchi I, Shigemi K, Kabuki Y, Hamasu K, Yamane H, Aoki M, et al. Central L-ornithine, but not polyamines, induces a hypnotic effect in neonatal chicks under acute stress. Nutr Neurosci 2010;13:17-20.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:343-353
DOI: 10.4274/BMJ.galenos.2021.83788

Research

Examination of Maternal-based Familial Factors in Malnourished Pediatric Patients Without Illness-Dependent Cause: A Single-center Case-control Study

Hastalığa Bağlı Nedeni Olmayan Malnütrisyonlu Pediatrik Hastalarda Anne Kaynaklı Ailesel Faktörlerin İncelenmesi: Tek Merkezli Olgu Kontrol Çalışması

Melike Ersoy[1], Sena Saygılı Ok[2], Semra Yılmaz[2], Tuğçe Çetin[3]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Metabolic Diseases, Istanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatric Child and Adolescent Psychiatry, Istanbul, Turkey
[3]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Istanbul, Turkey

ABSTRACT

Objective: Insufficient weight gain is one of the most common complaints in pediatric outpatient clinics in Turkey. This study aimed to investigate the effects of maternal psychiatric problems and familial factors on malnutrition in their children.

Methods: A total of 34 mothers of malnourished children aged 0 16 years, who applied to the pediatric metabolism outpatient clinic without underlying organic disease and mothers of healthy individuals from the same age and gender group were included in the study. Socio-demographic status, Symptom Checklist-90, multidimensional scale of perceived social support (MSPSS), and scale for domestic violence against women scales evaluation results of both groups were compared.

Results: An illness-dependent cause of malnutrition was not found in 34 of 127 (26.7%) patients. A statistical difference was found between the two groups in terms of educational status of parents, income level of the family, and work of the mother (p=0.008, p=0.039, p=0.009, and p=0.004, respectively). A statistical difference was found between the groups in terms of gestational week and the birth weight of the children (p=0.006 and p=0.011, respectively). The scores of cases who had planned pregnancy in the MSPSS were found to be statistically significantly higher than the cases without planned pregnancy (p=0.012). The rate of depression, somatization, obsession, sensitivity, and anxiety symptoms in cases with moderate or severe malnutrition severity was found to be statistically significantly higher than the cases with mild malnutrition (p=0.039, p=0.029, p=0.028, p=0.028, and p=0.011, respectively).

Conclusion: Parental education level, mother's working status, income level, mother's environmental support, and child's birth weight were determined as factors affecting the children's nutritional status, malnutrition type, and severity by causing effects on maternal psychology.

Keywords: Childhood malnutrition, maternal psychopathology, familial factors

ÖZ

Amaç: Yetersiz kilo alımı Türkiye'de çocuk polikliniklerine başvurularda en sık görülen şikayetlerden biridir. Bu çalışmada annenin psikopatolojik durumu ve ailesel faktörlerin çocuklardaki malnütrsiyona etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Pediyatrik metabolizma polikliniğine başvuran, altta yatan organik bir hastalığı olmayan 0-16 yaş arası malnütrisyonlu çocuğu olan 34 anne ile aynı yaş ve cinsiyet grubundan sağlıklı bireylerin anneleri çalışmaya dahil edildi. Her iki grubun sosyo-demografik durumları, Belirti Tarama testi-90, çok boyutlu algılanan sosyal destek ölçeği (ÇBASDÖ) ve kadına yönelik aile içi şiddet ölçeği (KYAİŞÖ) değerlendirme sonuçları karşılaştırıldı.

Bulgular: Anne ve babanın eğitim durumları, ailenin gelir düzeyi, annenin çalışması konularında her iki grup arasında istatistiksel anlamlı fark saptandı (p=0,008; p=0,039; p=0,009; p=0,004). Çocukların doğum haftası ile doğum kiloları arasında gruplar arası anlamlı fark saptandı

Address for Correspondence: Melike Ersoy, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Metabolic Diseases, Istanbul, Turkey
Phone: +0 212 414 20 00 E-mail: zeynepcey@hotmail.com ORCID ID: orcid.org/0000-0002-2316-0790

Cite as: Ersoy M, Saygılı Ok S, Yılmaz S, Çetin T. Examination of Maternal-based Familial Factors in Malnourished Pediatric Patients Without Illness-Dependent Cause: A Single-center Case-control Study. Med J Bakirkoy 2021;17:343-353

Received: 24.08.2021
Accepted: 09.11.2021

(p=0,006, p=0,011). Planlı gebelik yapan olguların anne ölçeği ÇBASDÖ alt boyutundan aldıkları puanlar, planlı gebelik yapmayan olgulara göre istatistiksel olarak anlamlı düzeyde yüksek saptandı (p=0,012). Manütrisyon ağırlığı orta/ağır olan olguların depresyon, somatizasyon, obsesyon, duyarlılık ve kaygı belirtilerinin yüksek olması oranı, hafif olan olgulara göre istatistiksel olarak anlamlı düzeyde yüksek saptandı (p=0,039, p=0,029, p=0,028, p=0,028, 0,011).

Sonuç: Ebeveyn eğitim düzeyi, annenin çalışması, gelir düzeyi, annenin çevre desteği ve çocuğun doğum tartısı, anne psikolojisinde etkiye yol açarak çocukların nütrisyonel durumu, malnütrisyon tipi ve ağırlığı üzerinde etkili faktörler olarak belirlenmiştir.

Anahtar Kelimeler: Çocukluk malnütrisyonu, anne psikopatolojisi, ailesel faktörler

INTRODUCTION

Malnutrition refers to deficient or excess nutrient intake, imbalanced essential nutrients, or impaired nutrient utilization, according to the definition of the World Health Organization (WHO), which is still a common and priority health problem in the world today. Malnutrition is one of the leading problems of childhood because it opens the door to other diseases and causes intelligence quotient regression in the long term (1,2). The bidirectional burden of malnutrition consists of both undernutrition and overweight and obesity, which is identified as diet-related non-communicable diseases. Undernutrition manifests in four broad forms: Wasting, stunting, underweight, and micronutrient deficiencies. Each form is expressed in the number of standard deviation (SD) units from the median of the WHO Child Growth Standards. Children are classified as malnourished if their z-scores are below minus two or minus three SD (-2 SD or -3 SD) from the median of the WHO Child Growth Standards. Wasting is defined as low weight-for-height, which refers to when a child's weight is lower than the weight ratio of a healthy child of the same height and indicates acute malnutrition. Traditionally, severity degree is determined as normal at 90-110%; mild at 80-90%, moderate at 70-80%, and severe at <70% according to Gomez scoring system, which usually occurs when a person has not had adequate quality and quantity of food. Stunting is defined as low height-for-age due to chronic or recurrent undernutrition that is usually associated with poverty, poor maternal health, and nutrition, frequent illness, and/or inappropriate feeding and care in early life. Stunting blocks children from reaching their expected physical and cognitive potential. Underweight is defined as low weight-for-age and the child may be stunted, wasted, or both. Micronutrient deficiencies are a lack of vitamins and minerals that are essential for body functions such as producing enzymes, hormones, and other substances needed for growth and neurocognitive development. This article will use malnutrition as common terminology that includes wasting, underweight, and stunning.

Approximately 45% of deaths among children under 5 years of age are linked to malnutrition that mostly occurs in low- and middle-income countries (3). Malnutrition is directly related to the deaths of 300,000 children annually and is indirectly responsible for the deaths of 5 million children under the age of 5. The prevalence of malnutrition varies between countries and even between regions of the same country. According to the 2020 data of the WHO, global stunting, underweight, and wasting prevalence under 5 years old is 21.3%, 13.5%, and 6.9%, respectively (4).

Food allergies, cystic fibrosis, malabsorption syndromes, genetic anomalies, inherited metabolic diseases, celiac disease, frequent recurrent infections, and immune deficiency syndromes are the leading medical causes (5,6). Social, developmental, economic, and poor maternal psychological may cause insufficient calorie intake apart from illness-dependent causes (7,8). Sometimes, more than one cause appears together. Malnutrition is a health problem; however, it may base on complex reticulated social problems. The cause-effect relationship becomes more complicated to resolve.

This study aimed to examine the relationship between maternal-based familial factors and malnutrition in pediatric patients.

METHODS

Participants

This is a single-center prospective study, which includes children who are admitted to the pediatric metabolism outpatient clinic between January 2021 and June 2021. Children aged 0-16 years whose height and weight measurements were -2 SD score (SDS) and those whose mothers volunteered for the study were included in the study. The control group consists of mothers of healthy individuals with age and gender-matched. Socio-demographic status, symptom checklist-90 (SCL-90), multidimensional scale of perceived social support (MSPSS), and scale for domestic violence against women (SDVAW) scales evaluation results of both groups were compared.

Socio-demographic Data and Scales

The individual and familial history and the developmental and Socio-demographic characteristics of cases were

determined using a form that was prepared by the researchers and filled in by the interviewer at the interview.

1. SCL-90-R

The SCL-90-R is one of the most widely used and well-validated self-report scales to assess a broad range of psychological problems and symptoms of psychopathology (9). The scale was translated and adapted to Turkish by Dağ (10).

The scale consists of 90 items using a 5-point scale (1 means "no problem" to 5 means "very serious") to measure the extent to which they have experienced the listed symptoms. The scale consists of 10 different subscales as follows: somatization, obsessive-compulsive disorder (OCD), interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid thought, psychoticism, and additional items.

The subscale scores are obtained by summing the scores of the answers given to the relevant items and dividing them by the number of items that make up that subscale. After adding the ratings (0-4 points) for each item for 90 items, the overall symptom level average is obtained by dividing the total score obtained by 90. Total and subscale scores are 0-4, and higher scores on the SCL-90-R indicate greater psychological distress. Parameters with a score >1 are considered high and an indication of important psychological problems.

2. MSPSS

MSPSS is a self-report measure of subjectively assessed social support that was developed by Zimet et al. (11). MSPSS is a 12-item self-assessment scale that has three subgroups, each consisting of four items as a family, friends, and a private person. A 7-point Likert-type scoring scale is from 12-84, with higher scores indicating high perceived social support. The reliability and validity of the Turkish version were evaluated (12).

3. SDVAW

The SDVAW was developed by Kilic (13) to measure domestic violence against women. The scale consists of 50 items and 5 subscales that consist of 10 items each. Subscales are physical, emotional; verbal, economic, and sexual violence. The SDVAW is scored as 1-3 Likert types, 34 items are scored straight and 16 items are reverse scored with a total score of 50-150. The total score obtained from the whole scale indicates the level of domestic violence against women.

Statistical Analyses

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, SD, median, frequency, percentage, minimum, and maximum) were used in evaluating the study data. The conformity of the quantitative data to the normal distribution was tested using the Shapiro Wilk test and graphical examinations. Independent group t-test was used for the comparison of normally distributed quantitative variables between the two groups and the Mann-Whitney U for comparisons between two groups of non-normally distributed quantitative variables. The Kruskal-Wallis and Dunn Bonferroni tests were used to compare the groups of more than two quantitative variables without normal distribution. The Pearson Chi-square, Fisher Exact, and Fisher-Freeman-Halton Exact test were used to compare qualitative data. The Pearson correlation analysis and Spearman correlation analysis were used to evaluate the relationships between quantitative variables. Statistical significance was accepted as a p-value of <0.05.

The study protocol was approved by the Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approved number: 2021/58; date: 01.02.2021). All patients agreed to participate in the study and written informed consents were obtained from each participant.

RESULTS

An illness-dependent cause of malnutrition could not be found in 34 of 127 (26.7%) patients who applied to the outpatient clinic with the complaint of insufficient weight gain. The ratio of children who are underweight, wasting, and stunting was 32.3%, 41.2%, and 26.5%, respectively. The study is summarized with a flow chart, in Figure 1. The severity score of the cases as mild, moderate, and severe were 55.9%, 35.3%, and 8.8%, respectively. The mean age of the mothers participating in the study was 35.02 ± 6.03 years (range, 20-52). Group of malnourished cases (n=34) and a group of healthy cases (n=51) were compared according to the specified scales.

Comparison of Socio-demographic Parameters According to Groups

A statistically significant difference was found between the two groups in the educational status of parents, income level of the family, and the working status of the mother ($p=0.008$, $p=0.039$, $p=0.009$, and $p=0.004$, respectively). The rate of mothers of malnourished cases not going to school was found to be significantly higher, as well as the rate of mothers of the control group having a university degree. The rate of being a university graduate from the fathers of the control group was found to be significantly higher

than those in the malnourished group. The rate of receiving wages below the minimum wage in the malnourished group was found to be significantly higher than those in the control group.

The rate of mothers of the malnourished group as housewives was found to be significantly higher, whereas the working rate of mothers of the control group was found to be significantly higher. No significant difference was found between the two groups in terms of age at marriage, age at first mother, and the number of children (Table 1).

Distribution and Significance of Parameters Related to the Child by Groups

Birth weights of patients in the malnourished group were statistically significantly lower than those in the control group (p=0.006). In addition, a statistically significant difference was found between the delivery times of the cases according to the groups (p=0.011). The rate of preterm birth at the time of delivery was found to be significantly higher in the malnourished group, whereas the rate of term birth was found to be significantly higher in the control group (Table 2).

MSPSD, SDVAW, and SCL-90 total and Subscale Scores Comparison of the Two Groups

No significant differences were observed between the two groups in terms of SDVAW (p=0.685), SCL-90 total (p=0.551), and subscales scores. However, the MSPSD scores of the mothers of the malnourished group were found to be statistically significantly lower compared to that

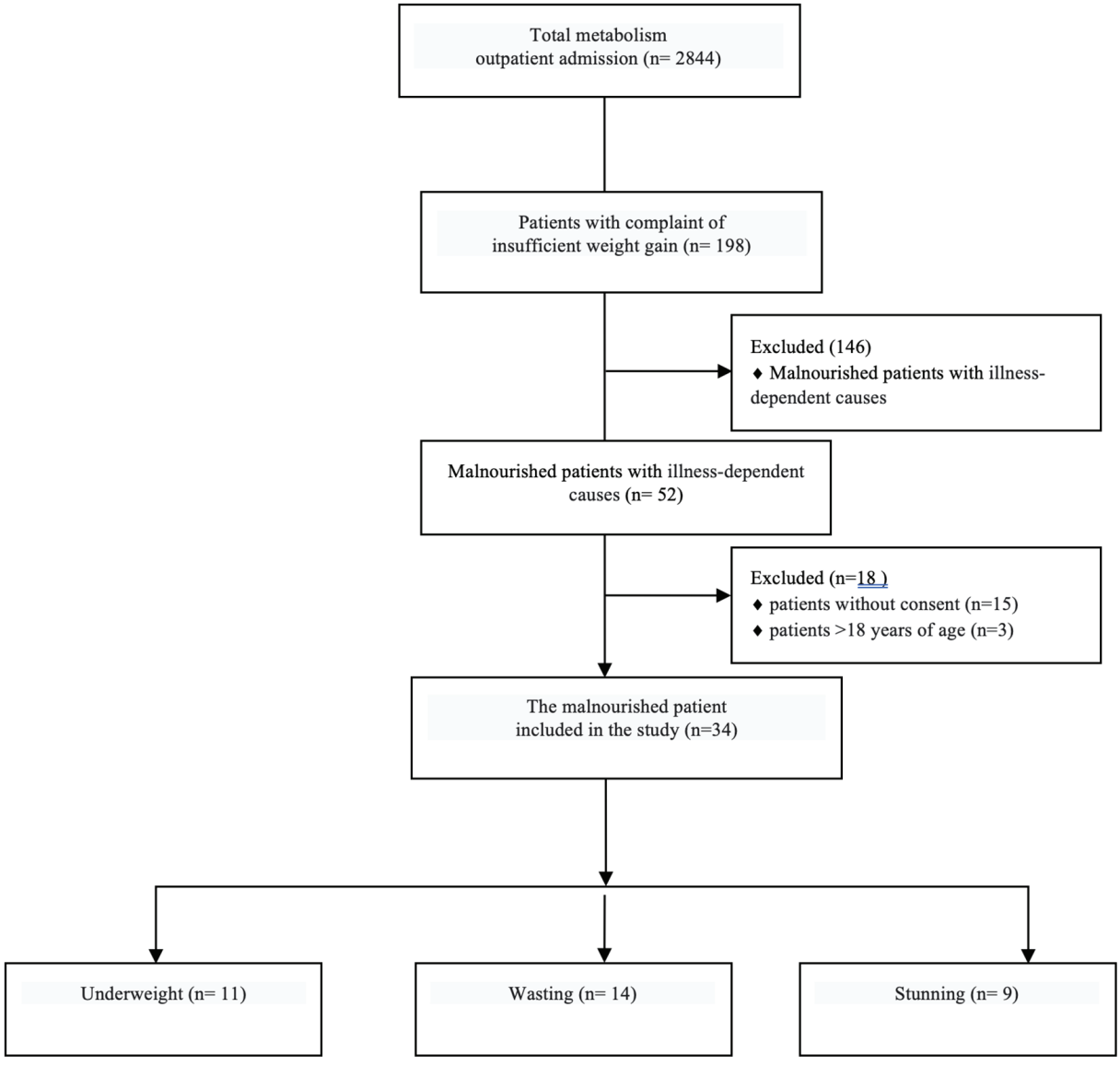

Figure 1. Study flow diagram

of the control group (p=0.031). In addition, the frequency of mothers with high scores on the anxiety subscale of the SCL-90 was found to be significantly higher in the malnourished group (Table 3).

Correlation of Mother Scale Scores and Child Parameters in Malnourished Cases Group

A statistical difference was found between the SCL-90 phobic anxiety subscale score of mothers of term and

Table 1. Comparison of sociodemographic parameters according to groups

		Malnourished (n=34)	Control (n=51)	p
Age (year)	**Mean ± SD**	35.41±6.67	34.76±5.62	0.631
	-	36.5 (20-49)	34.0 (22-52)	-
Mother education; n (%)	**None**	7 (20.6)	2 (3.9)	**0.008****
	Primary school	21 (61.8)	25 (49.0)	-
	High school	4 (11.8)	10 (19.6)	-
	University	2 (5.9)	14 (27.5)	-
Father education; n (%)	**None**	4 (11.8)	1 (2.0)	**0.039***
	Primary school	22 (64.7)	26 (51.0)	-
	High school	6 (17.6)	12 (23.5)	-
	University	2 (5.9)	12 (23.5)	-
Mother working; n (%)	**Housewife**	31 (91.2)	35 (68.6)	**0.009****
	Full time	1 (2.9)	10 (19.6)	-
	Shift	0 (0.0)	5 (9.8)	-
	Retired	2 (5.9)	1 (2.0)	-
Father working; n (%)	**Housewife**	7 (20.6)	4 (7.8)	0.078
	Full time	21 (61.8)	33 (64.7)	-
	Shift	1 (2.9)	9 (17.6)	-
	Retired	5 (14.7)	5 (9.8)	-
Marital status; n (%)	**Married**	33 (97.1)	47 (92.2)	0.644
	Divorced	1 (2.9)	4 (7.8)	-
Income status; n (%)	**Below minimum wage**	8 (23.5)	1 (2.0)	**0.004****
	Minimum wage	12 (35.3)	14 (27.5)	-
	Minimum wage -3000	4 (11.8)	15 (29.4)	-
	3000-5000	7 (20.6)	8 (15.7)	-
	≥5000	3 (8.8)	13 (25.5)	-
People live with; n (%)	**Nuclear family**	25 (73.5)	39 (76.5)	0.925
	Extended family	6 (17.6)	9 (17.6)	-
	Single parent with children	3 (8.8)	3 (5.9)	-
Marriage age	Mean ± SD	21.38±5.19	22.88±4.56	0.164
	Median (min-max)	20 (13-38)	22 (15-34)	-
Maternal age	Mean ± SD	23.82±5.48	24.92±4.75	0.329
	Median (min-max)	24 (16-40)	24 (17-35)	-
Number of siblings	Mean ± SD	2.76±1.35	2.27±0.98	0.075
	Median (min-max)	3 (1-7)	2 (1-5)	-

*p<0.05, **p<0.01, SD: Standart deviation, Min: Minimum, Max: Maximum, SD: Standart deviation, Min: Minimum, Max: Maximum

preterm children in the malnourished group. Cases with preterm birth time in the phobic anxiety subscale were found higher than cases with term birth time. In addition, the MSPSD score of the mothers who had a planned pregnancy was found to be statistically significantly higher than the cases who did not have a planned pregnancy (p=0.012).

Comparison of the type of Malnutrition and MSPSD, SDVAW, SCL-90 Total, and Subscale Scores in the Malnourished Group

No relationship was found between MSPSD, SDVAW, SCL-90 Total scores, and type of malnutrition. However, scores of the hostility subscale significantly differ according to the type of malnutrition (p=0.016). According to the pairwise comparisons. Hostility subscale scores of the cases with the malnutrition type stunting were found to be significantly higher than the cases with the malnutrition type underweight.

Comparison of Malnutrition Severity and MSPSD, SDVAW, SCL-90 Total, and Subscale Scores in the Malnourished group

No statistical difference was found between the mild and moderate/severe groups in MSPSD, SDVAW, and SCL-90 total scores. However, depression subscale scores were found to be statistically significantly higher in mothers of moderate/severe cases compared to those with mild malnutrition (p=0.039). In addition, the frequency of mothers with high scores on the somatization, OCD, interpersonal sensitivity, and anxiety subscale of the SCL-90 was found to

Table 2. Distribution and significance of parameters related to the child by groups

		Malnourished (n=34)	Control (n=51)	p
Gender; n (%)	Female	16 (47.1)	26 (51.0)	0.723
	Male	18 (52.9)	25 (49.0)	-
Child's birth order; n (%)	First	9 (26.5)	25 (49.0)	0.115
	Median	5 (14.7)	5 (9.8)	-
	Last	20 (58.8)	21 (41.2)	-
Planned pregnancy; n (%)	No	10 (29.4)	12 (23.5)	0.544
	Yes	24 (70.6)	39 (76.5)	-
Maternal psychiatric support status; n (%)	No	31 (91.2)	48 (94.1)	0.679
	Yes	3 (8.8)	3 (5.9)	-
Care at 0-3 months; n (%)	Mother	29 (85.3)	36 (70.6)	**0.143**
	Mother + caregiver	0 (0.0)	5 (9.8)	-
	Mother + grandparents	5 (14.7)	10 (19.6)	-
Breastfeeding duration; n (%)	None	1 (2.9)	1 (2.0)	0.420
	<3 mths	3 (8.8)	4 (7.8)	-
	3-6 mths	6 (17.6)	2 (3.9)	-
	6-12 mths	6 (17.6)	11 (21.6)	-
	12-24 mths	14 (41.2)	25 (49.0)	-
	≥24 mths	4 (11.8)	8 (15.7)	-
Birth weight (n=66)	Mean ± SD	2704.19±874.54	3223.43±508.69	**0.006****
	Median (min-max)	2800 (1050-4500)	3200 (2200-4500)	-
Type of delivery; n (%)	NSVD	7 (20.6)	20 (39.2)	0.071
	CS	27 (79.4)	31 (60.8)	-
Birth week; n (%)	Term	24 (70.6)	45 (88.2)	**0.011***
	Preterm	10 (29.4)	4 (7.8)	-
	Postterm	0 (0.0)	2 (4.0)	-

*p<0.05, **p<0.01, SD: Standart deviation, Min: Minimum, Max: Maximum

be significantly higher in the malnourished group (Table 4).

Correlation of Socio-demographic Characteristics with Malnutrition Severity

The rate of the education level of the fathers of moderate/severe cases as a primary school or below was found to be statistically significantly higher than the fathers of mild cases (p=0.005).

The comparison of the two groups in terms of the income level found a significantly high rate of "minimum wage" in moderate/severe cases (p=0.037) (Table 5).

DISCUSSION

Our study compared the mothers of malnourished children with the mothers of the control group in terms of socio-demographic characteristics, social support, domestic violence, and psychiatric symptoms.

Insufficient weight gain is one of the common reasons for pediatric outpatient clinic visits. Our study found no illness-related organic cause, including micronutrient deficiencies, in approximately one-fourth (26.7%) of the patients who were diagnosed with malnutrition. Therefore, revealing the

Table 3. MSPSD, SDVAW and SCL-90 total and subscale scores comparison of the two groups

TOTAL		Malnourished (n=34)	Control (n=51)	p
MSPSD	Mean ± SD	52.97±19.61	62.45±17.74	**0.031***
	Median (min-max)	55.50 (19-84)	61 (19-84)	-
SDVAW	Mean ± SD	74.24±8.90	73.53±5.83	0.685
	Median (min-max)	76 (50-87)	73 (62-87)	-
SCL-90	Mean ± SD	0.71±0.62	0.59±0.51	0.551
	Median (min-max)	0.50 (0-2.2)	0.50 (0-2.3)	-
SUBSCALE		Malnourished (n=34)	Control (n=51)	p
		n (%)	n (%)	
SCL general symptom score	Normal	29 (85.3)	48 (94.1)	0.257
	High	5 (14.7)	3 (5.9)	-
Somatization	Normal	30 (88.2)	47 (92.2)	0.708
	High	4 (11.8)	4 (7.8)	-
Obsession	Normal	27 (79.4)	45 (88.2)	0.268
	High	7 (20.6)	6 (11.80)	-
Interpersonal sensitivity	Normal	27 (79.4)	47 (92.2)	0.107
	High	7 (20.6)	4 (7.80)	-
Depression	Normal	28 (82.4)	47 (92.2)	0.189
	High	6 (17.6)	4 (7.80)	-
Anxiety	Normal	29 (85.3)	50 (98.0)	**0.036***
	High	5 (14.7)	1 (2.0)	-
Hostility	Normal	29 (85.3)	48 (94.1)	0.257
	High	5 (14.7)	3 (5.90)	-
Phobic anxiety	Normal	31 (91.2)	51 (100.0)	0.061
	High	3 (8.8)	0 (0.0)	-
Paranoid thought	Normal	29 (85.3)	47 (92.2)	0.474
	High	5 (14.7)	4 (7.8)	-
Psychoticism	Normal	31 (91.2)	48 (94.1)	0.679
	High	3 (8.8)	3 (5.9)	-

*p<0.05, SD: Standart deviation, Min: Minimum, Max: Maximum, MSPSS: Multidimensional scale of perceived social support, SDVAW: Scale for domestic violence against women, SCL-90: Symptom checklist-90

Table 4. Comparison of malnutrition severity and MSPSD, SDVAW, SCL-90 total and subscales scores in the malnourished group

		Malnutrition Severity		
		Mild (n=19)	Moderate/Severe (n=15)	p
		n (%)	n (%)	
SCL general symptom score	**Normal**	18 (94.7)	11 (73.3)	0.146
	High	1 (5.3)	4 (26.7)	-
Somatization	**Normal**	19 (100.0)	11 (73.3)	**0.029***
	High	0 (0.0)	4 (26.7)	-
Obsession	**Normal**	18 (94.7)	9 (60.0)	**0.028***
	High	1 (5.3)	6 (40.0)	-
Interpersonal sensitivity	**Normal**	18 (94.7)	9 (60.0)	**0.028***
	High	1 (5.3)	6 (40.0)	-
Depression	**Normal**	17 (89.5)	11 (73.3)	0.370
	High	2 (10.5)	4 (26.7)	-
Anxiety	**Normal**	19 (100.0)	10 (66.7)	**0.011***
	High	0 (0.0)	5 (33.3)	-
Hostilitiy	**Normal**	18 (94.7)	11 (73.3)	0.146
	High	1 (5.3)	4 (26.7)	-
Phobic anxiety	**Normal**	19 (100.0)	12 (80.0)	0.076
	High	0 (0.0)	3 (20.0)	-
Paranoid thought	**Normal**	18 (94.7)	11 (73.3)	0.146
	High	1 (5.3)	4 (26.7)	-
Psychoticism	**Normal**	19 (100.0)	12 (80.0)	0.076
	Yüksek	0 (0.0)	3 (20.0)	-

*p<0.05, MSPSS: Multidimensional scale of perceived social support, SDVAW: Scale for domestic violence against women, SCL-90: Symptom checklist-90

underlying maternal-based familial factors opens up an important area in solving the problem.

Wasting is the most common type of malnutrition in our study group. Wasting, which is an indicator of acute malnutrition that has not yet become chronic, is seen more frequently unlike other countries and global data, shows that rapid treatment response can be obtained with the early diagnosis since most of the published data are from underdeveloped countries and Turkey is among the developing countries (14-16). In addition, our study is regional in nature and not general in Turkey. Mild malnutrition constitutes the majority of cases (55.9%) due to similar reasons in the degree of malnutrition that increases the expectation of a positive response in terms of treatment because severe malnutrition causes high morbidity and mortality and constitutes the basis for infectious and non-infectious deaths (17,18).

Many studies on the relationship between malnutrition and the educational level of parents were reported in the literature (19-21). The literature revealed that the education level was lower in parents of children with malnutrition compared to that of the control group due to the high level of education of mothers that will increase their interest and experience in feeding their children and feed their children more consciously. In addition, the comparison of the parents' education levels with the severity of malnutrition revealed that the father's education level was lower in moderate/severe cases. Unlike the education level of the mother, the education level of the father was found to be associated with both malnutrition in the child and the severity of the malnutrition in our study. Father's education is important because he is the decision-maker of the family and his decisions can have a significant impact on children's health (22).

Many studies in the literature have shown that the income level of the family is an important factor affecting malnutrition in the child (23,24). Our study showed that the income level of families of children with malnutrition was

Tablo 5. Correlation of sociodemographic characteristics with malnutrition severity

		Malnutrition Severity		p
		Mild (n=19)	Moderate-Severe (n=15)	
Age (year)	Mean ± SD	34.95±6.84	36±6.63	0.655
	Median (min-max)	34 (24-49)	38 (20-46)	-
Mother education; n (%)	**None**	4 (21.1)	6 (40)	0.584
	Primary school	11 (57.9)	7 (46.7)	-
	High school-University	4 (21.1)	2 (13.3)	-
Father education; n (%)	**None-primary school**	11 (57.9)	15 (100.0)	**0.005****
	High school-university	8 (42.1)	0 (0.0)	-
Mother working; n (%)	**Housewife**	18 (94.7)	13 (86.7)	0.716
	Full time	0 (0.0)	1 (6.7)	-
	Retired	1 (5.3)	1 (6.7)	-
Father working; n (%)	**No**	8 (42.1)	4 (26.7)	0.350
	Yes	11 (57.9)	11 (73.3)	-
Marital status; n (%)	**Married**	19 (100.0)	14 (93.3)	0.441
	Divorced	0 (0.0)	1 (6.7)	-
Income status; n (%)	**< Minimum wage**	6 (31.6)	2 (13.3)	**0.037***
	Minimum wage	3 (15.8)	9 (60)	-
	≥ Minimum wage	10 (52.6)	4 (26.7)	-
People live with; n (%)	**Nuclear family**	14 (73.7)	11 (73.3)	1.000
	Exteneded family	3 (15.8)	3 (20)	-
	Single parent with children	2 (10.5)	1 (6.7)	-
Marriage age	Mean ± SD	21.63±5.37	21.07±5.13	0.758
	Median (min-max)	20 (15-38)	20 (13-33)	-
Maternal age	Mean ± SD	23.42±5.48	24.33±5.63	0.637
	Median (min-max)	24 (17-40)	24 (16-34)	-
Number of siblings	Mean ± SD	2.84±1.42	2.67±1.29	0.943
	Median (min-max)	3 (1-7)	3 (1-5)	-

*p<0.05 , **p<0.01, SD: Standart deviation, Min: Minimum, Max: Maximum

lower than that of the control group. In addition, the income level of the moderate/severe group was lower in severe malnutrition than the group with mild malnutrition. These results suggest that low income is a significant risk factor that may affect the child's access to adequate food intake for growth and development that deepen the severity of malnutrition. Several studies have also shown that the young maternal age at birth and the number of children is associated with malnutrition (25,26). Our study did not find any difference between the two groups in terms of young maternal age at birth and the number of children.

Many studies have shown that low birth weight and preterm birth increase the risk of developing malnutrition in later life (27,28). Similar to the literature, we found that low birth weight in the malnourished group was statistically significantly higher than the cases in the control group (p=0.006). In addition, preterm birth was higher in the malnourished group, whereas term birth was higher in the control group, which was statistically significant (p=0.011). This is valid for babies who did not catch up with their peers expected at the age of two due to insufficient micronutrient support and lack of care (29,30). Prenatal care both for

maternal and infant health is also important. The quality and number of prenatal care received by pregnant women should also be increased to reduce the frequency of low-birth-weight babies.

Mother's mental health not only affects children's long-term emotional, cognitive, and behavioral state but also impacts the child's physical health and development. Studies have shown that healthy maternal behavior and attitude have an important role in providing healthy nutrition in children (31,32). Unlike the literature, the SCL-90 total and subscale scores did not differ between mothers of malnourished and control groups in our study. However, the frequency of getting a high score on the SCL-90 anxiety subscale in the mothers of the malnourished group was found to be statistically high (p=0.036). These findings drew attention to significantly higher anxiety levels of these mothers. In addition, mothers of children with moderate/severe malnutrition were found to have a frequency of getting high scores on the SCL-90 anxiety, somatization, OCD, and interpersonal sensitivity subscales, which suggest that psychiatric symptoms in the mother may not only cause malnutrition but also determines the severity of malnutrition.

Many studies have shown that the children of depressed mothers were at an increased risk of malnutrition (33,34). Our study found that SCL-90 depression subscale scores are higher in the mothers of the malnourished group but not significant, which may be due to the generally high prevalence of mental health problems among women in Turkey (35). However, the comparison of malnutrition severity and depression scores found that SCL-90 depression subscale scores were statistically significant in the moderate/severe group than that of the mild group, which shows that maternal depression impacts the child's malnutrition and determines the severity of malnutrition. Evaluating and intervening with the mothers of mildly malnourished children for depressive symptoms may prevent the worsening of malnutrition.

Studies have shown that insufficient social support is one of the risk factors for malnutrition in children (36,37). The MSPSD scores of the mothers of the malnourished group were found to be statistically significantly lower compared to that of the control group (p=0.031). Low social support is known to be associated with other psychiatric diseases, especially depression (38,39). Based on our findings above, low social support may affect malnutrition as a predisposition for psychiatric disorders in the mother, as well as its effect on child nutrition. Having social support is an important factor in recognizing and intervening in domestic violence. The effect of domestic violence on child malnutrition has been shown in many studies (40). Our study found no difference between the two groups in terms of domestic violence.

Study Limitations

The small sample size is a limitation of our study.

CONCLUSION

In most societies, mothers are primarily responsible for feeding young children, which is a challenging task that requires good mental health maintenance. Mothers' mental health problems can contribute to negative consequences for their children's health and well-being. Along with these findings, the education of parents, income level, social support, and mental health of the mother should be evaluated in the child presenting with malnutrition without an organic cause and should be directed for appropriate intervention.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approved number: 2021/58; date: 01.02.2021).

Informed Consent: All patients agreed to participate in the study and written informed consents were obtained from each participant.

Authorship Contributions

Concept: M.E., S.Y., Design: M.E., S.Y., Data Collection Processing: T.Ç., S.Y., M.E., Analysis or Interpretation: M.E., S.Y., S.S.O., Writing: M.E., S.S.O.

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. Ijarotimi OS. Determinants of Childhood Malnutrition and Consequences in Developing Countries. Curr Nutr Rep 2013;2:129-33.
2. Walker SP, Grantham-Mcgregor SM, Powell CA, Chang SM. Effects of growth restriction in early childhood on growth, IQ, and cognition at age 11 to 12 years and the benefits of nutritional supplementation and psychosocial stimulation. J Pediatr 2000;137:36-41.
3. Caballero B. Global patterns of child health: the role of nutrition. Ann Nutr Metab 2002;46 (Suppl)1:3-7.
4. UNICEF/WHO/World Bank Group joint child malnutrition estimates, Levels and Tends in Child Malnutrition https://www.who.int/nutgrowthdb/2018.

5. Pelletier DL, Frongillo EA Jr, Schroeder DG, Habicht JP. The effects of malnutrition on child mortality in developing countries. Bull World Health Organ 1995;73:443-8.
6. Hendricks KM, Duggan C, Gallagher L, Carlin AC, Richardson DS, Collier SB, et al. Malnutrition in hospitalized pediatric patients. Current prevalence. Arch Pediatr Adolesc Med 1995;149:1118-22.
7. Lucarelli L, Sechi C, Cimino S, Chatoor I. Avoidant/Restrictive Food Intake Disorder: A Longitudinal Study of Malnutrition and Psychopathological Risk Factors From 2 to 11 Years of Age. Front Psychol 2018;9:1608.
8. Silveira KB, Alves JF, Ferreira HS, Sawaya AL, Florêncio TM. Association between malnutrition in children living in slums, maternal nutritional status, and environmental factors. J Pediatr 2010;86:215-20.
9. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacology bulletin 1973:1;9:13-28.
10. Dağ I. Belirti Tarama Listesi (Scl-90-R)'nin Üniversite Öğrencileri için güvenirliği ve geçerliği [Reliability and validity of the Symptom Check List (SCL-90-R) for university students]. Türk Psikiyatri Dergisi 1991;2:5-12.
11. Zimet GD, Dahlem, NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 1998;52:30-41.
12. Eker D, Arkar H, Yaldız H. Factorial structure, validity, and reliability of revised form of the multidimensional scale of perceived social support. Türk Psikiyatri Dergisi 2001;12:17-25.
13. Kilic B. The determination of violence against domestic women and the role of the nurse. (Master's Thesis). Istanbul: Istanbul University: 1999.
14. Das S, Fahim SM, Islam MS, Biswas T, Mahfuz M, Ahmed T. Prevalence and sociodemographic determinants of household-level double burden of malnutrition in Bangladesh. Public Health Nutr 2019;22:1425-32.
15. Khambalia AZ, Lim SS, Gill T, Bulgiba AM. Prevalence and sociodemographic factors of malnutrition among children in Malaysia. Food Nutr Bull 2012;33:31-42.
16. Hossain S. Chowdhury PB, Biswas RK, Hossain A. Malnutrition status of children under 5 years in Bangladesh: A sociodemographic assessment. Children and Youth Service 2020;117.
17. Kwena AM, Terlouw DJ, de Vlas SJ, Phillips-Howard PA, Hawley WA, Friedman JF, et al. Prevalence and severity of malnutrition in pre-school children in a rural area of western Kenya. Am J Trop Med Hyg 2003;68(4 Suppl):94-9.
18. Maitland K, Berkley JA, Shebbe M, Peshu N, English M, Newton CR. Children with severe malnutrition: can those at highest risk of death be identified with the WHO protocol? PLoS Med 2006;3:e500.
19. Gupta MC, Mehrotra M, Arora S, Saran M. Relation of childhood malnutrition to parental education and mothers' nutrition related KAP. Indian J Pediatr 1991;58:269-74.
20. Islam MR, Rahman MS, Rahman MM, Nomura S, de Silva A, Lanerolle P, et al. Reducing childhood malnutrition in Bangladesh: the importance of addressing socio-economic inequalities. Public Health Nutr 2020;23:72-82.
21. Tette EM, Sifah EK, Nartey ET. Factors affecting malnutrition in children and the uptake of interventions to prevent the condition. BMC Pediatr 2015;15:189.
22. Deshmukh PR, Sinha N, Dongre AR. Social determinants of stunting in rural area of Wardha, Central India. Med J Armed Forces India 2013;69:213-7.
23. Hong R. Effect of economic inequality on chronic childhood undernutrition in Ghana. Public Health Nutr 2007;10:371-8.
24. Davey S, Davey A, Adhish SV, Bagga R. Study of impact of sociocultural and economic factors of mothers on the nutritional status of their malnourished children in a rural area of Delhi, India. Int. J. Public Health 2015;4:162-7.
25. Wemakor A, Garti H, Azongo T, Garti H, Atosona A. Young maternal age is a risk factor for child undernutrition in Tamale Metropolis, Ghana. BMC Res Notes 2018;11:877.
26. Sezgin B, Akın A. Adölesan dönemi üreme sağlığı. Sağlık ve Toplum Dergisi 1998;34:27-36.
27. Barros FC, Huttly SR, Victora CG, Kirkwood BR, Vaughan JP. Comparison of the causes and consequences of prematurity and intrauterine growth retardation: a longitudinal study in southern Brazil. Pediatrics 1992;90(2 Pt 1):238-44.
28. Rahman A, Iqbal Z, Bunn J, Lovel H, Harrington R. Impact of maternal depression on infant nutritional status and illness: a cohort study. Arch Gen Psychiatry 2004;61:946-52.
29. Hollo O, Rautava P, Korhonen T, Helenius H, Kero P, Sillanpää M. Academic achievement of small-for-gestational-age children at age 10 years. Arch Pediatr Adolesc Med 2002;156:179-87.
30. Ounsted M, Moar VA, Scott A. Growth and proportionality in early childhood. III. Differences between babies of low birthweight in well-nourished and malnourished populations. Early Hum Dev 1986;14:167-78.
31. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet 2008;371:243-60.
32. Faruque AS, Ahmed AM, Ahmed T, Islam MM, Hossain MI, Roy SK, et al. Nutrition: basis for healthy children and mothers in Bangladesh. J Health Popul Nutr 2008;26:325-39.
33. Haithar S, Kuria MW, Sheikh A, Kumar M, Vander Stoep A. Maternal depression and child severe acute malnutrition: a case-control study from Kenya. BMC Pediatr 2018;18:289.
34. Surkan PJ, Kennedy CE, Hurley KM, Black MM. Maternal depression and early childhood growth in developing countries: systematic review and meta-analysis. Bull World Health Organ 2011;89:608-15.
35. Kose T. Gender, income and mental health: The Turkish case. PLoS One 2020;15:e0232344.
36. Adekunle L. The effect of family structure on a sample of malnourished urban Nigerian children. Food Nutr Bull 2005;26:230-3.
37. Rikimaru T, Yartey JE, Taniguchi K, Kennedy DO, Nkrumah FK. Risk factors for the prevalence of malnutrition among urban children in Ghana. J Nutr Sci Vitaminol 1998;44:391-407.
38. Hefner J, Eisenberg D. Social support and mental health among college students. Am J Orthopsychiatry 2009;79:491-9.
39. Ünal S, Küey L, Güleç C, Bekaroğlu M, Evlice YE, Kırlı S. Depresif Bozukluklarda Risk Etkenleri. Klinik Psikiyatri 2002;5:8-15.
40. Sobkoviak RM, Yount KM, Halim N. Domestic violence and child nutrition in Liberia. Soc Sci Med 2012;74:103-11.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:354-358
DOI: 10.4274/BMJ.galenos.2021.80774

Research

Percutaneous Cholecystostomy as a Step or Final Treatment for Acute Cholecystitis

Akut Kolesistit Tedavisinde Perkütan Kolesistostomi Bir Basamak Mı? Yoksa Nihai Bir Tedavi Mi?

Alpen Yahya Gümüşoğlu[1], Hamit Ahmet Kabuli[1], Aysun Erbahçeci Salık[2], Çağlayan Çakır[3], Seymur Abdullayev[4], Kıvanç Derya Peker[5], Mehmet Karabulut[1], Gökhan Tolga Adaş[1]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
[2]Linköping University Hospital, Clinic of Radiology, Linköping, Sweden
[3]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey
[4]Doğa Hospital, Clinic of General Surgery, Istanbul, Turkey
[5]University of Health Sciences Turkey, Başaksehir Çam and Sakura Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey

ABSTRACT

Objective: This study aimed to investigate the effectiveness of percutaneous cholecystostomy (PC) as a step treatment in patients who underwent PC for acute cholecystitis.

Methods: Data of 248 patients who underwent PC for acute cholecystitis between January 2015 and December 2019 were retrospectively analyzed. All patients who underwent PC were evaluated for a distal transition by cholangiography taken by the interventional radiology department in the third week after discharge. In addition, all patients were re-evaluated by the anesthesia department. Patients were retrospectively evaluated in terms of age, gender, American Society of Anesthesiologists physical status (ASA-PS) class, surgical procedure, complications after PC, and termination of PC.

Results: A total of 231 patients were included in the study. The mean age of patients was 68.6 (minimum-maximum: 32-92 years) and the male/female ratio was 1.04. The anesthesia evaluation of the patients categorized 44 patients (19.05%) as ASA-PS class I-II and 187 (80.95%) as ASA-PS III-IV. A total of 17 (7.35%) patients died in the 30-day follow-up period. The examination of the remaining patient revealed that PC was used as a step treatment in the transition to elective cholecystostomy in 106 (45.8%) patients, whereas 108 (50.4%) had it as a final treatment method since an operation is impossible. The median follow-up period in these patients was 2.6 years. Recurrent cholecystitis developed in 14 (12.96%) patients in the group who underwent PC.

Conclusion: PC should be noted as an alternative step treatment method for acute cholecystitis but maybe a final treatment option in patients with high comorbidity.

Keywords: Percutaneous cholecystostomy, acute cholecystitis, ASA-PS

ÖZ

Amaç: Bu çalışmada akut kolesistit tanısı ile perkütan kolesistostomi uygulanan hastaların verileri incelenerek yüksek riskli hastalarda perkütan kolesistostomi tedavisinin sonuçlarını araştırmayı hedefledik.

Gereç ve Yöntem: Bu çalışmada Ocak 2015-Aralık 2019 tarihleri arasında akut kolesistit nedeniyle perkütan kolesistostomi uygulanan 248 hastanın hastaların verileri retrospektif olarak değerlendirildi. Perkütan kolesistostomi uygulanan tüm hastalar taburculuk sonrası üçüncü haftada girişimsel radyoloji tarafından çekilen kolanjiyografi ile distale geçiş açısından değerlendirildi, aynı zamanda tüm hastalar yeniden anestezi tarafından değerlendirildi. Hastaların yaş, cinsiyet, Amerikan Anestezistler Derneği'nin fiziksel durumu (ASA-PS) class, yapılan cerrahi işlem, perkütan kolesistostomi sonrası gelişen komplikasyonlar ve perkütan kolesistostomi sonlandırılma durumları retrospektif olarak değerlendirildi.

Bulgular: Toplam 231 hasta çalışmaya dahil edildi. Hastalarda ortalama yaş 68,6 (minimum-maksimum: 32-92/yıl), erkek/kadın oranı: 1,04 idi. Kırk dört hastanın anestezi değerlendirilmesi (%19,05) ASA-PS sınıf I-II, 187 (%80,95) hastanın ise ASA-PS III-IV olarak saptanmıştır. Hastaların

Address for Correspondence: Alpen Yahya Gümüşoğlu, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of General Surgery, Istanbul, Turkey
Phone: +90 535 307 83 91 E-mail: alpenygumus@hotmail.com ORCID ID: orcid.org/0000-0001-5378-9074

Cite as: Gümüşoğlu AY, Kabuli HA, Erbahçeci Salık A, Çakır Ç, Abdullayev A, Peker KD, Karabulut M, Adaş GT. Percutaneous Cholecystostomy as a Step or Final Treatment for Acute Cholecystitis. Med J Bakirkoy 2021;17:354-358

Received: 28.08.2021
Accepted: 11.10.2021

30 günlük takibinde 17 (%7,35) hastada mortalite izlenmiştir. Geriye kalan hastalar incelendiğinde 106 (%45,8) hastada perkütan kolesistostomi elektif kolesistostomiye geçişte basamak tedavisi olarak yer alırken, 108 (%50,4) hasta da cerrahi uygulanamadığından nihai bir tedavi yöntemi olarak kullanılmıştır. Bu hastalarda medyan takip süresi 2,6 yıldır. Perkütan kolesistostomi ile tedavi edilen grupta 14 (%12,96) olguda rekürren kolesistit atağı gelişdi.

Sonuç: Perkütan kolesistostomi,akut kolesititte alternatif olarak basamak amaçlı tedavi yöntemi olmakla beraber komorbiditesi yüksek hastalarda nihai bir tedavi seçeneği olabileceği bilinmelidir.

Anahtar Kelimeler: Perkütan kolesistotomi, akut kolesistit, ASA-PS

INTRODUCTION

Acute cholecystitis is an emergency that is seen in 20% of patients with gallstone disease (1,2). The percutaneous cholecystostomy (PC) can be applied as a step treatment to prepare patients with high comorbidity for laparoscopic cholecystectomy (3). Studies are claiming that PC is a final treatment method (4). However, consensus on this issue is unclear.

This study aimed to determine the effectiveness of PC as a step treatment or a final treatment method by retrospectively evaluating the cases that were treated with PC in our clinic.

METHODS

In this study, data of 248 patients, who underwent PC with acute cholecystitis diagnosis between January 2015 and December 2019, were retrospectively analyzed. Patients who underwent PC due to gallbladder perforation were excluded from the study. A total of 17 patients, whose clinical and demographic data were missing, were excluded from the study. Consent was obtained from all patients who participated in the study. This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Ethics Committee (number: 2020-14-10 date: 06.07.2020).

A treatment approach was applied to patients with acute cholecystitis within certain study protocols since a hepatopancreatobiliary surgery unit has been available in our clinic since 2013. Therefore, all patients presenting with acute cholecystitis underwent early laparoscopic cholecystectomy under the Tokyo 18/13 Guidelines. The Tokyo Guidelines were adopted for the classification of violence for acute cholecystitis diagnosis (5). The anesthesia risk was determined by the anesthesia department before the surgery for patients with high comorbidities according to the American Society of Anesthesiologists physical status classification (ASA-PS) (6). According to the Tokyo guidelines, percutaneous cholecystectomy treatment was applied to the group with severity grades 2 and 3 and a high risk of anesthesia (ASA-PS III-IV). The biliary trees of all patients who underwent PC are evaluated by cholangiography taken by the interventional radiology department in the third week after discharge. After the sixth week, laparoscopic cholecystectomy was applied to the patients, which was re-evaluated by the anesthesia department and had no contraindications for surgery. The ASA-PSIV patient group with high anesthesia risk was grouped into two. As a result of cholangiography, the percutaneous catheter was withdrawn in the group with a cystic duct open distal transition, whereas in the group with symptoms with no distal transition and closed catheter, cholecystostomy catheter revision was performed at 3-month intervals (Figure 1). The patients' age, gender, ASA scores, surgical procedures, complications after PC, and PC terminations or revisions were retrospectively evaluated.

PC Method and Follow-up

Diagnosis of acute cholecystitis was confirmed by ultrasonography (US) and/or computed tomography. All procedures were performed with US guidance by a dedicated interventional radiologist under standard sterile conditions with local anesthesia and intravenous sedation. Most are performed in the interventional radiology unit, but procedures of 7 patients were performed in the intensive care unit due to unstable vital signs. The transhepatic approach was preferred for all the procedures and the gallbladder was always punctured using the Seldinger technique. Access to the gallbladder was confirmed by bile aspiration and an 8-12 Fr pigtail catheter was placed in the gallbladder lumen. Procedures were completed after confirmation of the pigtail loop of the catheters in the gall bladder lumen by the US. After the procedure, catheters were sutured to the skin and placed on gravity drainage. After 3 weeks of follow-up, transcatheter cholangiography (TC) was performed to assess the patency of the cystic and common bile ducts and the position of the catheter. When the cystic duct patency and tract maturation were confirmed by TC and the patient was asymptomatic, the catheters were withdrawn. Contrarily, if a patent cystic canal could not be observed, patients were followed up for 2 more weeks and the TC was performed again after 2 weeks. Within 2 weeks interval, patients were evaluated using the TC until cystic canal patency and tract maturation was verified up to

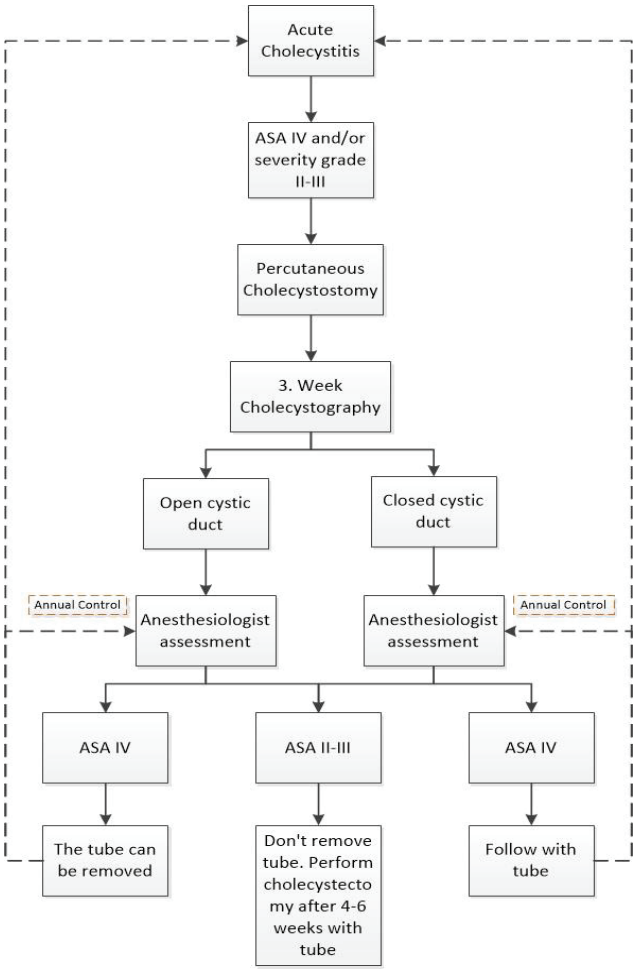

Figure 1. Our PC algorithm
PC: Percutaneous cholecystostomy, ASA: American Society of Anesthesiologists

3 months, and catheters were changed after 3 months. After 3 months of drainage, the catheters were discontinued in patients with cystic ducts and they were followed 3 days when the patient was asymptomatic and well-tolerated 3 days with stopped drainage, then the catheters were withdrawn. In case of symptoms for 3 days follow-up, patients were followed with percutaneous catheters, and catheters were exchanged with 3 months interval.

RESULTS

Data from 248 patients were analyzed within the scope of the study. A total of 17 patients with missing data were excluded from the study. The mean age of patients was 68.6 (minimum-maximum: 32-92), and the male/female ratio was 1.04. The anesthesia evaluation categorized 44 patients (19.05%) as ASA-PSI-II and 187 (80.95%) as ASA-PS III-IV. Considering the severity classification of patients according to Tokyo 2018 guidelines, 144 patients were grade 2 and 87 patients were grade 3. The technical success rate was 100% during the study period; however, the clinical success rate was 92.65%, and septic signs and symptoms could not be resolved despite PC in 17 (7.35%) patients who were hospitalized in the ICU. These patients died from severe sepsis during the 30-day follow-up period.

During the follow-up period, 101 patients underwent laparoscopic cholecystectomy and 5 patients underwent open cholecystectomy. The remaining 108 (50.46%) patients were treated with the PC. The median follow-up period for these patients was 2.6 years. Recurrent cholecystitis occurred in 14 (12.96%) patients. PC catheters could be withdrawn in 68 patients upon seeing a distal transition in the cystic canal. During the follow-up of the remaining 40 patients, the distal transition was seen in 21 patients in a 3-week follow-up in the first 3 months, or the PC catheters could be withdrawn since they were asymptomatic when the catheter was closed. In the remaining 19 patients, catheter changes were performed once in 13 patients, twice in 2 patients, three times in 1 patient, and four times in 3 patients at 3-month intervals.

The most frequent complications following the PC procedure were catheter replacement (1.73%), catheter discontinued (1.29%), bile leak (1.29%), fistula to skin (0.86%), abscess/infection (0.86%), and bleeding (1.73%) (Table 1).

Table 1. Demographic information and complications

• Age, years, median (range)	68.6 (32-92)
• Gender, n (%)	
• Females	113 (48.9%)
• Males	118 (51.1%)
Complication	
• Bile leak	3 (1.29%)
• Bleeding	4 (1.73%)
• Catheter dislodgement, replaced	4 (1.73%)
• Catheter dislodgement, discontinued	3 (1.29%)
• Fistula to skin	2 (0.86%)
• Abscess formation/infection	2 (0.86%)

DISCUSSION

Laparoscopic cholecystectomy is a successful and effective treatment method for acute cholecystitis. PC can be used as a step treatment for elective cholecystectomy in some cases (3). In addition, PC can be used as an alternative treatment method with low complication rates especially in patients with high surgical risk (4,7).

The current study performed PC as a step treatment in the transition to elective cholecystostomy in 45.8% of patients, whereas 50.4% of patients had it as final treatment since no surgery could be performed. PC was the final treatment method especially in patients with a high risk of anesthesia and not suitable for elective surgery. The study of Tolan et al. (4) revealed PC as the final treatment method with a rate of 57.5%. Similar to the present study, PC was used as the ultimate treatment method in 55.9% of patients in the study by Pang et al. (7).

A total of 17 patients with critical septic findings in the intensive care unit did not respond to the PC and the post-procedure septic findings did not improve. Response to PC ranges from 56-100% in the literature (8-11). This ratio is better in the present study. It is considered that patients' poor treatment responses may be due to the presence of severe comorbidities and possible multiple foci of infection. Therefore, the gallbladder drainage may not be sufficient to rule out septic findings. In addition, acute cholecystitis diagnosis in this group of patients is often more difficult because of their severe concomitant systemic diseases.

Cholecystectomy was performed in 106 (45.8%) patients who underwent percutaneous drainage, wherein 94 (88.6%) underwent laparoscopic cholecystectomy and 7 (6.6%) laparoscopic partial cholecystectomy, whereas 5 (4.7%) underwent cholecystectomy with the transition to open. The study by Yeo et al. (12) performed cholecystectomy in 42 (41%) patients. The conversion rate was 15% in the study, whereas 34 (81%) patients underwent laparoscopic cholecystectomy.

In the present study, the rate of recurrence after PC was 12.96%, whereas this rate was 22% in the study of Sanjay et al. (13). The study of Chang et al. (14) observed recurrent acute cholecystitis in 7 high-risk patients (11.7%). The remaining patients (88.3%) were successfully treated with PC alone. The study by Wang et al. (15) revealed a recurrence rate of 9.2% and suggested that the cause of recurrence was complicated cholecystitis and elevated white blood cell counts.

The literature stated that the average time for PC removal is 4-6 weeks (16). In the present study, cholangiography evaluation was preferred in the third week in cases who underwent PC. Peroperative PC catheter was withdrawn in cases where cholecystectomy was planned, whereas in 68 cases who had a distal transition on cholangiography but could not be operated on due to high risk, the catheter was removed in the third week with the confidence given by cholecystostomy performed by the transhepatic way. However, due to the distal transition on cholangiography in 40 patients with high surgical risk, percutaneous catheter replacement was performed in these cases at 3-month intervals. Recurrent PC catheter replacement was reported to be applied in the study by Boules et al. (17). The study of Horn et al. (18) revealed that recurrence is more frequently observed in cases where the distal transition is not observed (21.1% versus 36.7%; p=0.037). Therefore, catheter revision was followed in this high-risk group with no distal transition in cholangiography and symptoms in closely follow-up (18). In addition, PC catheters can be left in place in patients with calculous cholecystitis and poor life expectancy. The catheter in this patient group was preferred to be removed but was tried to be withdrawn safely if possible during follow-up. Three months later, when the catheter replacement was first planned, the catheter drainage was closed and patients were followed up for 3 days. During these 3 days, symptoms, US findings, and clinical signs were not observed, thus the catheters were withdrawn.

In the present study, PC was performed using the transhepatic method. The aim was to choose a method with a lower risk of bile leakage, peritonitis, and intra-abdominal organ injury, as well as easier catheter stabilization in the group of patients with high comorbidity. However, this method resulted in pneumothorax and bleeding more frequently than transperitoneal PC (19). In the 30-day follow-up of patients, a total of 17 (7.35%) patients died. In addition, complication rates were compatible with the literature in terms of catheter replacement (1.73%), catheter discontinuation (1.29%), bile leak (1.29%), fistula to skin (0.86%) abscess/infection (0.86%), and bleeding (1.73%) (20).

In cases where a distal transition is not seen in the cholangiography, methods such as cystic duct percutaneous stent placement and gallstone removal with fluoroscopy can be used to prevent recurrence in cases where the catheter cannot be withdrawn. Our study excluded such cases can be considered a limiting feature. The retrospective design of the study is another feature that limits the study (21,22).

CONCLUSION

In patients with high surgical risk in the treatment of acute cholecystitis, PC is seen as a final treatment method rather than a treatment step. However, further studies are needed to reduce the risk of recurrence.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Ethics Committee (number: 2020-14-10 date: 06.07.2020).

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

Authorship Contributions

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

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. Strasberg SM. Clinical practice. Acute calculous cholecystitis. N Engl J Med 2008;358:2804-11.
2. Keus F, Gooszen HG, van Laarhoven CJ. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. Cochrane Database Syst Rev 2010;2010:CD008318.
3. Okamoto K, Suzuki K, Takada T, Strasberg SM, Asbun HJ, Endo I, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci 2018;25:55-72.
4. Tolan HK, Semiz Oysu A, Başak F, Atak İ, Özbağrıaçık M, Özpek A, et al. Percutaneous cholecystostomy: A curative treatment modality forelderly and high ASA score acute cholecystitis patients. Ulus Travma Acil Cerrahi Derg 2017;23:34-8.
5. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2018;25:41-54.
6. ASA Physical Status Classification System. Last approved bythe ASA House of Delegates on October 15, 2014.
7. Pang KW, Tan CH, Loh S, Chang KY, Iyer SG, Madhavan K, et al. Outcomes of Percutaneous Cholecystostomy for Acute Cholecystitis. World J Surg 2016;40:2735-44.
8. Akhan O, Akinci D, Ozmen MN. Percutaneous cholecystostomy. Eur J Radiol 2002;43:229-36.
9. Boland GW, Lee MJ, Leung J, Mueller PR. Percutaneous cholecystostomy in critically ill patients: early response and final outcome in 82 patients. AJR Am J Roentgenol 1994;163:339-42.
10. Chopra S, Dodd GD 3rd, Mumbower AL, Chintapalli KN, Schwesinger WH, Sirinek KR, et al. Treatment of acute cholecystitis in non-critically ill patients at high surgical risk: comparison of clinical outcomes after gallbladder aspiration and after percutaneous cholecystostomy. AJR Am J Roentgenol 2001;176:1025-31.
11. Browning PD, McGahan JP, Gerscovich EO. Percutaneous cholecystostomy for suspected acute cholecystitis in the hospitalized patient. J Vasc Interv Radiol 1993;4:531-7; discussion 537-8.
12. Yeo CS, Tay VW, Low JK, Woon WW, Punamiya SJ, Shelat VG. Outcomes of percutaneous cholecystostomy and predictors of eventual cholecystectomy. J Hepatobiliary Pancreat Sci 2016;23:65-73.
13. Sanjay P, Mittapalli D, Marioud A, White RD, Ram R, Alijani A. Clinical outcomes of a percutaneous cholecystostomy for acute cholecystitis: a multicentre analysis. HPB (Oxford) 2013;15:511-6.
14. Chang YR, Ahn YJ, Jang JY, Kang MJ, Kwon W, Jung WH, et al. Percutaneous cholecystostomy for acute cholecystitis in patients with high comorbidity and re-evaluation of treatment efficacy. Surgery 2014;155:615-22.
15. Wang CH, Wu CY, Yang JC, Lien WC, Wang HP, Liu KL, et al. Long-Term Outcomes of Patients with Acute Cholecystitis after Successful Percutaneous Cholecystostomy Treatment and the Risk Factors for Recurrence: A Decade Experience at a Single Center. PLoS One 2016;11:e0148017.
16. Park JK, Yang JI, Wi JW, Park JK, Lee KH, Lee KT, et al. Long-term outcome and recurrence factors after percutaneous cholecystostomy as a definitive treatment for acute cholecystitis. J Gastroenterol Hepatol 2019;34:784-90.
17. Boules M, Haskins IN, Farias-Kovac M, Guerron AD, Schechtman D, Samotowka M, et al. What is the fate of the cholecystostomy tube following percutaneous cholecystostomy? Surg Endosc 2017;31:1707-12.
18. Horn T, Christensen SD, Kirkegård J, Larsen LP, Knudsen AR, Mortensen FV. Percutaneous cholecystostomy is an effective treatment option for acute calculous cholecystitis: a 10-year experience. HPB (Oxford) 2015;17:326-31.
19. Little MW, Briggs JH, Tapping CR, Bratby MJ, Anthony S, Phillips-Hughes J, et al. Percutaneous cholecystostomy: the radiologist's role in treating acute cholecystitis. Clin Radiol 2013;68:654-60.
20. Stanek A, Dohan A, Barkun J, Barkun A, Reinhold C, Valenti D, et al. Percutaneous cholecystostomy: A simple bridge to surgery or an alternative option for the management of acute cholecystitis? Am J Surg 2018;216:595-603.
21. Comin JM, Cade RJ, Little AF. Percutaneous cystic duct stent placement in the treatment of acute cholecystitis. J Med Imaging Radiat Oncol 2010;54:457-61.
22. Kim YH, Kim YJ, Shin TB. Fluoroscopy-guided percutaneous gallstone removal using a 12-Fr sheath in high-risk surgical patients with acute cholecystitis. Korean J Radiol 2011;12:210-5.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:359-366
DOI: 10.4274/BMJ.galenos.2021.59354

Research

Prognostic Performance of the CALL Score in Hospitalized Patients with COVID-19 Pneumonia

COVID-19 Pnömonisi Tanısı ile Yatarak Tedavi Gören Hastalarda CALL Skorun Prognostik Performansı

Işıl Kibar Akıllı[1], Müge Bilge[2]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Chest Disease, Istanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Internal Medicine, Istanbul, Turkey

ABSTRACT

Objective: Scoring systems are frequently used to predict disease severity and mortality in many different clinical conditions. The prognostic significance of a new scoring system developed for patients who are hospitalized due to Coronavirus disease-2019 (COVID-19) pneumonia, which is named CALL that stands for comorbidity (C), age (A), lymphocyte count (L), and lactate dehydrogenase (LDH) (L), was evaluated.

Methods: This is a retrospective and observational study on 582 patients who were hospitalized due to moderate or severe COVID-19 pneumonia after being diagnosed as positive using the real-time polymerase chain reaction testing. CALL scores were evaluated in the two groups of patients, namely the survivors and the non-survivors.

Results: Among all patients, 339 (58.24%) were males and 272 (46.73%) were older than 60 years. Comorbidities were not found in 174 (29.89 %) patients, whereas 408 (70.11%) had one or more comorbidities, mainly hypertension (n=275, 47.25%), diabetes mellitus (n=192, 32.98%), and coronary artery disease (n=78, 13.4%). Class A consist of 113 (19.41%) patients (4-6 s), 219 (37.62%) in Class B (7-9 s), and 250 (42.95%) in Class C (10-13 s). In-hospital mortality was found to be 6% (35 cases). Only 1 (0.88%) patient in Class A and 27 (10.8%) in Class C were deceased. As a result, in-hospital mortality was observed as 27 patients in Class C and 1 in Class A. The receiver operating characteristic analysis was used to assess the performance of the CALL score; the area under the curve was 0.76 (95% confidence interval of 0.68-0.85). Using a cutoff value of 10 points, the sensitivity was 77% and specificity was 60% for predicting in-hospital mortality.

Conclusion: CALL score was observed to be strongly related to in-hospital mortality. As a simple diagnostic measure, it may be used as a complementary score for the treatment planning and management of COVID-19 pneumonia in pandemic conditions.

Keywords: CALL score, COVID-19 pneumonia, comorbidity, age, lymphocyte, LDH, mortality

ÖZ

Amaç: Hastalık şiddetinin belirlenmesi ve prognozun öngörülmesinde çeşitli skorlama sistemleri kullanılmaktadır. Mevcut çalışmada, Koronavirüs hastalığı-2019 (COVID-19) pnömonisinde yüksek riskli hastaların saptanması amacı ile geliştirilen, 4 parametreden oluşan ve CALL skor C: komorbidite, A: yaş, L: lenfosit sayısı ve L: laktat dehidrojenaz (LDH) olarak adlandırılan, yeni bir skor sisteminin sonucu öngörebilme yetisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 1 Eylül 2020-31 Aralık 2020 tarihleri arasında yatarak tedavi gören, Ters transkripsiyon polimeraz zincir reaksiyonu testi ile doğrulanmış, orta ve ağır şiddetli COVID-19 pnömonisi olan hastaların tıbbi kayıtlarının retrospektif analizi yapıldı. Çalışmaya toplam 582 hasta dahil edildi. CALL skoru sonuçları sağ kalanlar ve kaybedilenler olmak üzere iki hasta grubu için karşılaştırıldı.

Bulgular: 339 (%58,24) erkek hastanın olduğu çalışmada, 272 (%46,73) hastanın 60 yaş üzerinde olduğu saptandı. 174 (%29,89) hastada herhangi bir komorbidite bulunmazken 408 (%70,11) hastada bir veya daha fazla komorbidite olduğu gözlendi. Komorbiditeler arasında ilk üç sırada hipertansiyon (275, %47,25), diyabet (192, %32,98) ve koroner arter hastalığı (78, %13,4) yer almaktaydı. CALL skoru sınıflamasına göre; 113 (%19,41) hasta sınıf A (4-6 puan), 219 (%37,62) hasta sınıf B (7-9 puan) ve 250 (%42,95) hasta sınıf C (10-13 puan) olarak kaydedildi. Sınıf A'da sadece 1 (%0,88) hastanın, sınıf C'de ise 27 (%10,8) hastanın kaybedildiği saptandı. Hastane içi mortalite oranı %6 (35 hasta) bulundu. Kaybedilen toplam 35 hasta değerlendirildiğinde; 27 hastanın sınıf C, 7 hastanın sınıf B ve 1 hastanın sınıf A kategorisinde bulunduğu gözlendi. CALL skorun performansını değerlendirmek amacı ile kullanılan Receiver operating characteristics analizinde arena eğri altında 0,76 (%95 güven aralığı, 0,68-

Address for Correspondence: Işıl Kibar Akıllı, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Chest Disease, Istanbul, Turkey
Phone: +90 542 345 04 13 E-mail: isilkibar@yahoo.com ORCID ID: orcid.org/0000-0000-000-000

Cite as: Kibar Akıllı I, Bilge M. Prognostic Performance of the CALL Score in Hospitalized Patients with COVID-19 Pneumonia. Med J Bakirkoy 2021;17:359-366

Received: 29.08.2021
Accepted: 09.11.2021

0,85) bulundu. Cutoff değeri 10 puan olarak kabul edildiğinde, CALL skorun hastane içi mortaliteyi öngörmede %77 duyarlılık ve %60 özgüllüğe sahip olduğu saptandı.

Sonuç: CALL skorun hastane içi mortalite ile güçlü bir şekilde ilişkili olduğu gözlendi. CALL skoru, özellikle pandemi koşulları dikkate alındığında COVID-19 pnömonisinin tedavi yönetiminde basit, yardımcı ve tamamlayıcı bir skor olarak kullanılabilir.

Anahtar Kelimeler: CALL skor, COVID-19 pnömonisi, komorbidite, yaş, lenfosit, LDH, mortalite

INTRODUCTION

The novel coronavirus Severe Acute Respiratory syndrome-coronavirus-2 (SARS-CoV-2), which was declared as an epidemic by the World Health Organization in March 2020, continues to be a life-threatening problem worldwide. SARS-CoV-2 appears in various clinical forms, such as rapidly progressing hypoxemia and acute respiratory distress syndrome, viral pneumonia, and/or cytokine storm that lead to a consequent hyperinflammatory state and death (1). Coronavirus disease-2019 (COVID-19) progresses with higher mortality among elderly patients with comorbidities, such as diabetes, hypertension, cardiovascular disease, and cerebrovascular disease (2). Early identification of patients who may develop critical illness is of great importance and may support appropriate treatment delivery and resources optimization.

Several known scoring systems are being used in the management of patients with many critical conditions, and the process of patient care, hospitalization, or admission to the intensive care unit (ICU) can be decided based on these scores (3). New scoring systems are still being developed for COVID-19, one of which is the CALL score by Ji et al. (4) that was derived based on patients' comorbidities (C), age (A), lymphocyte count (L), and serum lactate dehydrogenase (LDH) levels (L) at admission. CALL was developed to identify a patient group at high risk of disease progression. Advanced age (>60 years), high level of LDH, and low lymphocyte count (<1.0 × 109/L) are independent high-risk factors for the progression of COVID-19, and the CALL score contributes to its prediction (4). Studies have shown that the newly developed predictive model, CALL score for COVID-19, may predict disease progression and in-hospital deaths (4-6).

This retrospective study aimed to develop a metric that would specifically incorporate the information related to comorbidity, thus the CALL score was used to predict COVID-19 hospital mortality. The classification method, which was widely accepted in many former studies in the literature was based on survivors/non-survivors, thus using the same classification system was preferred. However, we further investigated these patients in two groups with a more graded classification system as A, B, and C.

METHODS

Study Design and Cohort

This single-center, cross-sectional retrospective study was conducted at our hospital in Istanbul, Level-3 pandemic, which included 986 patients who are confirmed for COVID-19 from September 1, 2020, to December 31, 2020. Demographic data (age and gender), vital signs as heart rate, respiratory rate, and blood pressure, oxygen saturation (SpO_2), and mean oxygen requirement at hospitalization duration, comorbidity status, laboratory parameters including complete blood count, c-reactive protein, procalcitonin, cardiac enzymes, coagulation profile, D-dimer, liver and renal functions, LDH, and arterial blood gas results of patients were collected. Nasal and pharyngeal swabs yielding real-time-polymerase chain reaction results, thoracic computerized tomography (CT) results, and clinical outcomes (mortality, discharge, and hospitalization period), as well as comorbidities, were recorded. Patients with incomplete data and pregnant women were excluded from the study. Patients who did not have any clinical or laboratory data or who had pneumonia arising from other causes were excluded from the study. After the exclusion, 582 patients (≥18 years) who were hospitalized with the diagnosis of moderate or severe COVID-19 pneumonia were included in the study. None was admitted to the ICU. The data was categorized as moderate or severe based on severity classification regarding the "Chinese Guidelines for Diagnosis and Treatment of Novel Coronavirus Pneumonia" (Trial Version 7) (7). Patients with moderate COVID-19 had a fever (>37.3 °C) and respiratory symptoms identified by radiological findings that suggest pneumonia. The existence of any one of the following criteria was assumed to be a sufficient condition to consider the patient as severe: (1) respiratory distress (≥30 breaths/min), (2) oxygen saturation of ≤93% at rest, and (3) arterial partial pressure of oxygen /fraction of inspired oxygen of ≤300 mmHg (1 mmHg: 0.133 kPa). CT scans were obtained from all patients during hospital admission. CT results were classified as mild, moderate, and severe involvement by an expert radiologist (8). Comorbidity was defined as the presence of at least one of the following: hypertension, diabetes, cardiovascular disease, chronic lung disease (Asthma and chronic obstructive pulmonary disease), chronic liver disease, human

immunodeficiency virus infection, or at least 6 months of active malignancy (4). CALL score was calculated for each patient from the retrospectively obtained data as follows: no comorbidity = 1 point; comorbidity = 4; age of ≤60=1 and >60=3; lymphocyte of >1.0 × 10^9/L=1 and ≤1.0 × 10^9/L=3; and LDH of ≤250 U/L=1, 250-500 U/L=2, and >500 U/L=3 points. CALL score was classified as class A with 4-6 points, wherein patients show <10% probability of progression and were considered as low risk; class B with 7-9 points, wherein patients have 10%-40% probability of progression and at intermediate risk; and class C with 10-13 points, wherein patients have >50% probability of progression and at high risk (4).

The primary endpoint was defined as the in-hospital death. All cases that are enrolled in the study were managed according to the "COVID 19 treatment protocol of the Turkish Health Ministry" (9). The research was first registered in the data of the "Turkish Health Ministry Scientific Research Committee" and then reviewed and approved by the Local Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (no: 2021-05-10, date: 01.03.2021).

Statistical Analysis

All statistical analyses were performed in commercially available Statistical Package for the Social Sciences software version 21 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Patient characteristics were summarized using descriptive statistics. Continuous variables were compared using either the unpaired t-test to compare two variables or a one-way analysis of variance to compare multiple variables. Categorical variables were compared using the Chi-square test. The Mann-Whitney U test was used to evaluate continuous variables with the non-normal distribution. A p-value of <0.05 was accepted as statistically significant. Receiver operating characteristic (ROC) analysis was carried out to identify an index for the prediction of in-hospital death.

RESULTS

Baseline data characterizing the patients and their comorbidities are given in Table 1. Laboratory measurements, CT results, and disease severity are presented in Table 2. CALL score components and classifications are shown in Tables 3 and 4, respectively. Among 582 patients, 408 (70.11%) had comorbidities that mainly include hypertension (n=275, 47.25%), diabetes mellitus (n=192, 32.98%), and coronary artery disease (n=78, 13.4%). Based on established categories, 251 (43.12%) patients were classified as moderate and 331 (56.88%) as severe. Pulmonary involvement in the thorax CT was mild in 125 (21.47%), moderate in 258 (44.32%), and severe in 199 (34.21%) patients. Class A consists 113 (19.41%) patients (4-6 points), 219 (37.62%) in class B (7-9 points), and 250 (42.95%) in class C (10-13) (Table 4). In addition, 181 patients (54.69 %) with severe disease were found in class C and 39 (11.78%) in class A.

The clinical characteristics of survivor and non-survivor groups were compared. No statistically significant difference was found between genders; however, 25 (71.42 %) patients who died were male. Comorbidity, age, LDH, and lymphocyte as components of the CALL score were significantly different between the two groups based on univariate analyses.

In addition to comorbidity numbers, respiratory rate, oxygen saturation, supplemental oxygen requirement, heart rate, urea, albumin, troponin-I, disease severity, and thorax CT score were found to be significantly different between the two groups. Duration of hospitalization was 11.26±5.89 days in survivors, whereas 11.8±7.29 days in non-survivors and was insignificant. In-hospital mortality was found to be 6% (35 cases), wherein 34 (97.15%) cases were severe.

The median age was 71.57±13.56 years in non-survivors, whereas 59.39±14.51 years in survivors (p<0.001). Among all patient, 26 (74.28%) were deceased and were older than 60 years (p=0.001), 30 (85.72%) had at least one comorbidity, and 22 (62.87%) had two or more comorbidities. As expected, members of the non-survivor group were older and had more comorbidities (p<0.001 and p=0.04, respectively). Comorbid hypertension, congestive heart failure, cerebrovascular disease, and malignancy were significantly more common in non-survivors than those in survivors (p=0.01, p=0.01, p=0.002, and p=0.005, respectively). In 25 (71.43%) of the deceased patients, the lymphocyte count was found to be 1.0×10^9/L or less and in 10 (28.57%) and was >1.0×10^9/L in 15 patients (p<0.001). In the non-survivor group, LDH was <250 U/L in 6 (17.14%), 250-500 U/L in 20 (57.14%), and >500 U/L in 9 patients (25.72%) (p=0.01).

In the deceased group, 34 (97.15%) were severe, whereas only 1 patient (2.85%) was moderate. In this group, according to the thorax CT findings, moderate involvement was found in 11 (31.42%) and severe involvement was found in 23 (65.73%) cases. Therefore, deceased patients had significantly higher disease severity status and thorax CT scores compared to survivors (p<0,001). Of 582 patients, 113 (19.41%) were in class A, 219 (37.62%) in class B, and 250 (42.95%) in class C. Class C had 27 (10.8%) deceased patients, whereas 1 (0.88%) in class A. Out of 250 patients, 181 (72.4%) in class C were severe.

Table 1. Evaluation of baseline characteristics and comorbidities for survivors and nonsurvivors

	Survivors (n=547)	Non-survivors (n=35)	p
Age, years	59.39±14.51	71.57±13.56	<0.001
Sex male, 339 (58.24%)	314 (57.4%)	25 (71.42%)	NS
Body temperature, °C	36.87±0.63	36.93±0.7	NS
Systolic blood pressure, mmHg	127.18±18.86	133.14±19.13	NS
Diastolic blood pressure, mmHg	71.54±10.60	72.31±10.58	NS
Heart rate, per minute	84.23±16.18	90.05±20.15	0.04
Respiratory rate, per min	20.70±4.34	29.91±4.59	<0.001
SpO_2 (median; under oxygen support)	94.51±1.98	92.62±2.45	<0.001
O_2 support, L/per min	3.66±5.47	13.45±8.35	<0.001
Comorbidities, n (%)			
Arterial hypertension 275 (47.25)	251 (45.88)	24 (68.57)	0.01
Diabetes mellitus 192 (32.98)	179 (32.72)	13 (37.14)	NS
Coronary artery disease 78 (13.4)	71 (12.97)	7 (20)	NS
Congestive heart failure 27 (4.63)	22 (4.02)	5 (14.28)	0.01
Cerebrovascular disease 17 (2.92)	12 (2.19)	5 (14.28)	0.002
Asthma 49 (8.41)	46 (8.40)	3 (8.57)	NS
COPD¶ 17 (2.92)	16 (2.92)	1 (2.85)	NS
Malignancy 29 (4.98)	23 (4.20)	6 (17.14)	0.005
Chronic kidney disease 28 (4.81)	26 (4.75)	2 (5.71)	NS

¶COPD: Chronic obstructive pulmonary disease

Univariate analysis showed that age older than 60 years [odds ratio (OR): 3.53, 95% confidence interval (CI): 1.62-7.68] and lymphocyte count of ≤1.0×10⁹/L (OR: 5.90, 95% CI: 2.53-13.74) were associated with mortality. ROC analysis was used to assess the performance of the CALL model; the area under the curve (AUC) was 0.76 (95% CI: 0.68-0.85, p<0.001) (Figure1). Using a cutoff value of 10 points, sensitivity was 77% and specificity was 60% in predicting in-hospital mortality.

Therefore, mortality was associated with advanced age (>60 years), presence of certain comorbidities (hypertension, congestive heart failure, cerebrovascular disease, and malignities), higher LDH, lower lymphocyte, and higher CALL scores. In addition, mortality was found to be associated with lower oxygen saturation, tachypnea, need for supplemental oxygen support, high urea, troponin-I, low albumin levels, disease severity status, and thorax CT score.

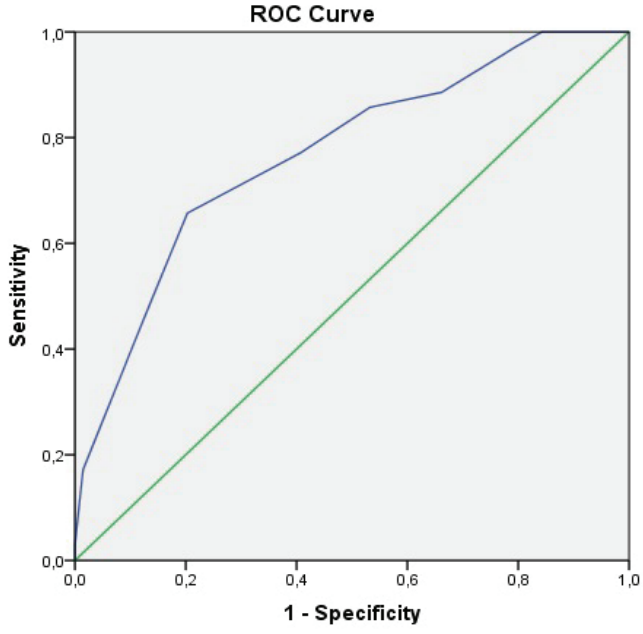

Figure 1. ROC curve for CALL score in predicting mortality. AUC 0.76 (95% CI: 0.68-0.85).

ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

DISCUSSION

Considering the high infectivity and mortality rates of COVID-19 with pneumonia, early disease diagnosis is essentially critical. Blood tests and simple scoring systems

play an important role in the early diagnosis, considering the information they provide to physicians regarding the inflammatory process.

Previous studies reported that advanced age, lymphopenia, and high-level LDH were correlated with worse outcomes and mortality (10-18). Contrarily, the presence of comorbidity as an independent risk factor is still controversial. However, several studies claimed that the presence of comorbidities was an independent risk factor (10,12,19-22). CALL score was first defined by Ji et al. (4) who excluded severe patients in their cohort. Contrarily, Kamran et al. (6) included severe and critical cases in their study and concluded that CALL score was a reliable indicator to predict the progression and mortality of disease although the presence of unaccompanied comorbidities was not an independent risk factor. Additionally, some studies have reported that comorbidity was not predictive for disease severity (6,23-26). Guan et al. (12) did not only report that patients with any comorbidity had worse clinical outcomes but also reported that the number of comorbidities was an important risk factor for composite outcomes (ICU admission, invasive ventilation, or death) (19).

Ucan et al. (27) determined that community-acquired pneumonia scores were more predictive of mortality and

Table 2. Evaluation of laboratory results, CT results, and disease severity for survivors and nonsurvivors

	Survivors (n=547)	Non-survivors (n=35, 6%)	p
Hematocrit, %	37.76±4.76	37.42±5.425	NS
Platelet, cells/mL	247.75±116.06	213.65±111.26	NS
Neutrophil, cells/mL	5.37±4.38	6.31±3.97	NS
Lymphocytes, cells/mL	1.22±0.57	0.84±0.58	<0.001
Glucose, mg/dL	148.88±68.33	164.04±79.26	NS
Urea, mg/dL	38.99±26.96	58.59±34.27	<0.001
Creatinine, mg/dL	0.96±0.74	1.00±0.41	NS
ALT, U/L	44.02±33.14	44.60±21.76	NS
AST, U/L	41.32±35.99	40.20±32.08	NS
Lactate dehydrogenase, U/L	336.63±139.10	421.60±221.96	0.001
C-reactive protein, mg/L	101.31±77.21	123.07±66.76	NS
Procalcitonin, ng/mL	0.41±0.50	1.01±1.64	NS
Ferritin, mcg/L	461.69±564.75	628.96±598.92	NS
D-dimer, mcg FEU/mL	0.70±1.02	1.01±1.01	NS
Fibrinogen, mg/dL	490.10±119.89	516.02±137.01	NS
INR	1.05±0.16	1.08±0.21	NS
Troponin-I, ng/mL	12.20±25.73	32.09±64.21	<0.001
Albumine, g/dL	36.54±5.86	32.70±5.68	<0.001
CT, n (%)	-	-	<0.001
Mild 125 (21.47)	124 (22.66)	1 (2.85)	-
Moderate 258 (44.32)	247 (45.15)	11 (31.42)	-
Severe 199 (34.21)	176 (32.19)	23 (65.73)	-
Disease severity status, n (%)	-	-	<0.001
Moderate, 251(43.12)	250 (45.7)	1 (2.85)	-
Severe, 331 (56.88)	297 (54.3)	34 (97.15)	-
Hospitalization, days	11.26±5.89	11.80±7.29	NS
Death, n (%)	-	35 (6%)	-

CT: Computerized tomography, ALT: Alanine transaminase, AST: Aspartate transaminase, INR: International normalized ratio

progression in COVID-19 than specific COVID-19 scoring systems, hence they suggested that the CALL score could be used to decide for outpatient management in COVID-19. Their study reported no deaths in CALL score class A (27). However, our study reported 1 (0.88%) patient who died in class A and 27 (10.8%) in class C. Ji et al. (4) also found in their study that >96% of participants did not progress to serious disease with CALL scores of 4-6 points (Class A).

Several studies showed that the CALL score was a powerful prognosticator to predict the progression to severe COVID-19, identify critically ill patients who require an ICU admission, in-hospital mortality, worsening illness, and associated fatality (5,6,26,28). Our study also demonstrated the high performance of the CALL model in predicting the disease severity and hospital mortality; the AUC was 0.76 (95% CI: 0.68-0.85) and using a cutoff value of 10 points, sensitivity was 77% and specificity was 60 % in predicting in-hospital mortality.

Moreover, another study showed that the CALL score performed well for 30-day mortality but not for 7-day ICU admission (29). Contrarily, Al Hassan et al. (25) showed that the CALL score had a poor discriminatory value for the composite outcome of ICU admission or death. Similarly, Shi et al. (30) stated that the CALL score performed poorly in predicting mortality and critical illness.

Recently, Cabanillas et al. (31) suggested that the CALL score was useful in managing the treatment of patients with COVID-19 and were able to prevent the development of respiratory failure by giving methylprednisolone treatment to high-risk patients, whom they identified with the CALL score (31). In addition, the "CALL-(interleukin)IL-6 score," which was created by adding IL-6 to the CALL score, showed a significantly better prediction of in-hospital mortality and progression to severity than the original CALL score (32).

Our study found older age, presence, and multiplicity of comorbidity, lymphopenia, and increased LDH levels to be strongly associated with mortality. In addition, increased respiratory rate, lower oxygen saturation, severe disease status, and higher thorax CT scores were found to be associated with death. CALL score proved to be a reliable prognosticator for mortality. Older age and the presence of comorbidity were thought to be associated with mortality.

Table 3. Components of CALL score

	Survivors (n=547)	Non-survivors (n=35, 6%)	p
Comorbidity numbers, n (%)	-	-	0.04
Without, 174 (29.89)	169 (30.89)	5 (14.28)	-
With, 408 (70.11)	378 (69.11)	30 (85.72)	-
With 1, 151 (25.94)	143 (26.14)	8 (22.85)	-
With ≥2, 257 (44.17)	235 (42.97)	22 (62.87)	-
Lymphocyte, n (%)			
>1×10⁹/L, 331 (56.87)	321(58.68)	10 (28.57)	-
≤1×10⁹/L, 251 (43.13)	226 (41.32)	25 (71.43)	<0.001
Age, n (%)			
>60 years, 272 (46.73)	246 (44.97)	26 (74.28)	0.001
≤60 years, 310 (53.27)	301 (55.03)	9 (25.72)	-
LDH, n (%)			
<250 U/L, 150 (25.77)	144 (26.32)	6 (17.14)	-
250-500 U/L, 365 (62.71)	345 (63.07)	20 (57.14)	-
>500 U/L, 67 (11.51)	58 (10.61)	9 (25.72)	0.01

LDH: Lactate dehydrogenase

CONCLUSION

CALL score achieved a significant predictor of mortality in COVID-19. Especially considering the pandemic conditions, the CALL model, which consists of only four clinical parameters, helps the clinician in predicting mortality and providing appropriate treatment with its high accuracy and easy-to-use features. The ambiguity of results in several studies on CALL scores may vary due to sample sizes or demographic differences. Nevertheless, prospective multi-centered studies in extensive demographic samples are needed to confirm the CALL score and reveal the role of comorbidities.

Table 4. CALL score classification

	Mortality		Disease Severity		p
CALL Score (Points)	Non-survivors n=35 (6%)	Survivors n=547 (94%)	Moderate n=251 (43.12%)	Severe n=331 (56.87%)	
Class A (4-6 s) n=113 (19.41%)	1 (0.88)	112 (99.11)	74 (65.48)	39 (34.51)	p<0.001
Class B (7-9 s) n=219 (37.62%)	7 (3.19)	212 (96.80)	108 (49.31)	111 (50.68)	
Class C (10-13 s) n=250 (42.95%)	27 (10.8)	223 (89.2)	69 (27.6)	181 (72.4)	

ETHICS

Ethics Committee Approval: The research was first registered in the data of the "Turkish Health Ministry Scientific Research Committee" and then reviewed and approved by the Local Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (no: 2021-05-10, date: 01.03.2021).

Informed Consent: This retrospective study.

Authorship Contributions

Surgical and Medical Practices: I.K.A., M.B., Concept: I.K.A., M.B., Design: I.K.A., M.B., Data Collection or Processing: I.K.A., M.B., Analysis or Interpretation: I.K.A., M.B., Literature Search: I.K.A., M.B., Writing: I.K.A., M.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. World Health Organization timeline-COVID-19. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#event-71. Accessed 31 June 2021.
2. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect 2020;80:e14-8.
3. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ 2020;369:m1328.
4. Ji D, Zhang D, Xu J, Chen Z, Yang T, Zhao P, et al. Prediction for Progression Risk in Patients With COVID-19 Pneumonia: The CALL Score. Clin Infect Dis 2020;71:1393-9.
5. Grifoni E, Valoriani A, Cei F, Vannucchi V, Moroni F, Pelagatti L, et al. The CALL Score for Predicting Outcomes in Patients With COVID-19. Clin Infect Dis 2021;72:182-3.
6. Kamran SM, Mirza Z-H, Moeed HA, Naseem A, Hussain M, Fazal I, et al. CALL Score and RAS Score as Predictive Models for Coronavirus Disease 2019. Cureus [Internet]. 2020 Nov 7 [cited 2021 Aug 25]; Available from: https://www.cureus.com/articles/43938-call-score-and-ras-score-as-predictive-models-for-coronavirus-disease-2019.
7. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). Chin Med J (Engl) 2020;133:1087-95.
8. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. Radiol Cardiothorac Imaging 2020;2:e200047.
9. Republic of Turkey Ministry of Health. Covid-19 (SARS-CoV-2 Infection) Guide. Available @:covid-19rehberieriskinhastatedavisip df.pdf (saglik.gov.tr), (Accessed 20/07/2020.).
10. Stawicki SP, Jeanmonod R, Miller AC, Paladino L, Gaieski DF, Yaffee AQ, et al. The 2019-2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. J Glob Infect Dis 2020;12:47-93.
11. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int 2020;44:1792-7.
12. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-20.
13. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. J Infect Dis 2020;221:1762-9.
14. Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. Am J Emerg Med 2020;38:1722-6.
15. Shi J, Li Y, Zhou X, Zhang Q, Ye X, Wu Z, et al. Lactate dehydrogenase and susceptibility to deterioration of mild COVID-19 patients: a multicenter nested case-control study. BMC Med 2020 ;18:168.
16. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med 2020;180:1081-9.
17. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics. of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
18. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
19. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55:2000547.
20. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
21. Wendel Garcia PD, Fumeaux T, Guerci P, Heuberger DM, Montomoli J, Roche-Campo F, et al. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. EClinicalMedicine 2020;25:100449.
22. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
23. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
24. Zhang C, Qin L, Li K, Wang Q, Zhao Y, Xu B, et al. A Novel Scoring System for Prediction of Disease Severity in COVID-19. Front Cell Infect Microbiol 2020 ;10:318.
25. Al Hassan H, Cocks E, Jesani L, Lewis S, Szakmany T. Clinical Risk Prediction Scores in Coronavirus Disease 2019: Beware of Low Validity and Clinical Utility. Crit Care Explor 2020;2:e0253.
26. Olivares F, Muñoz D, Fica A, Delama I, Alvarez I, Navarrete M, et al. Clinical features of 47 patients infected with COVID-19 admitted to a Regional Reference Center. Rev Med Chil 2020;148:1577-88.
27. Ucan ES, Ozgen Alpaydin A, Ozuygur SS, Ercan S, Unal B, Sayiner AA, et al. Pneumonia severity indices predict prognosis in coronavirus disease-2019. Respir Med Res 2021;79:100826.
28. Xu W, Huang C, Fei L, Li W, Xie X, Li Q, et al. A Novel Prediction Model of COVID-19 Progression: A Retrospective Cohort Study. Infect Dis Ther 2021;10:1491-504.
29. Lazar Neto F, Marino LO, Torres A, Cilloniz C, Meirelles Marchini JF, Garcia de Alencar JC, et al. Community-acquired pneumonia

severity assessment tools in patients hospitalized with COVID-19: a validation and clinical applicability study. Clin Microbiol Infect 2021;27:1037.e1-1037.e8.

30. Shi Y, Pandita A, Hardesty A, McCarthy M, Aridi J, Weiss ZF, et al. Validation of pneumonia prognostic scores in a statewide cohort of hospitalised patients with COVID-19. Int J Clin Pract 202;75. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ijcp.13926.
31. Cabanillas F, Morales JG, Conde J, Bertrán-Pasarell J, Fernández R, Hernandez-Silva Y, et al. Single-Arm, Open-Label Phase 2 Trial of Preemptive Methylprednisolone to Avert Progression to Respiratory Failure in High-Risk Patients with COVID-19 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Mar [cited 2021 Aug 25]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.03.08.21253117.
32. Grifoni E, Vannucchi V, Valoriani A, Cei F, Lamanna R, Gelli AMG, et al. Interleukin-6 added to CALL score better predicts the prognosis of COVID-19 patients. Intern Med J 2021;51:146-7.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:367-374
DOI: 10.4274/BMJ.galenos.2021.35403

Research

Are Platelet-related Parameters Predictive of the Prognosis of Hodgkin's Lymphoma?

Hodgkin Lenfoma Prognozunda Platelet İlişkili Parameterler Prediktif Midir?

Aydan Akdeniz[1], Özgür Mehtap[2], Volkan Karakuş[3], Serkan Ünal[2], Kemal Aygün[2], Gülhan Örekici Temel[1], Anıl Tombak[1], Eyüp Naci Tiftik[1]

[1]Mersin University Faculty of Medicine, Department of Hematology, Mersin, Turkey
[2]Kocaeli University Faculty of Medicine, Department of Hematology, Kocaeli, Turkey
[3]Alaaddin Keykubat University Faculty of Medicine, Department of Hematology, Antalya, Turkey

ABSTRACT

Objective: Hodgkin's lymphoma has a good prognosis unless it has relapsed or become refractory. The predictive value of platelet (Plt)-related parameters, namely, mean Plt volume (MPV), plateletcrit (PCT), Plt distribution width, and Plt, is shown in some solid tumors and hematological malignancies, but it remains unknown in Hodgkin's lymphoma. This study aimed to define their values and effects on staging and relapsing status in patients with Hodgkin's lymphoma by comparing them with those in healthy subjects.

Methods: Values of Plt-related parameters of 217 patients with Hodgkin's lymphoma and 205 healthy individuals were documented and compared according to the disease stage and relapsing status. We defined the cutoff values for diagnosis, staging, and relapsing status of these parameters using the receiving operating characteristic curve analysis.

Results: For diagnosis, the cutoff values of MPV, Plt, and PCT were 8.49 fL, 32,1000/mm^3, and 0.31, respectively. For staging, the cutoff values of MPV and Plt were 9.5 fL and 12 fL, respectively. None of the parameters were associated with relapsing status.

Conclusion: This is the first study evaluating Plt-related parameters in Hodgkin's lymphoma. Further studies including survival analyses will clarify the effect of these parameters on Hodgkin's lymphoma.

Keywords: Hodgkin's lymphoma, platelet, MPV, PCT, PDW

ÖZ

Amaç: Hodgkin lenfoma nüks etmedikçe veya refrakter olmadıkça iyi prognoza sahiptir. Trombosit ilişkili parameterlerin (MPV, PCT, PDW, Plt) prediktif değeri bazı solid tümörlerde ve hematolojik malignitelerde gösterilmiştir, ancak Hodgkin lenfomada halen bilinmemektedir. Biz de çalışmamızda Hodgkin lenfomalı hastalarla sağlıklı bireylerde bu parameterlerin düzeylerini karşılaştırarak tanısal değerleri ile evreleme ve nüks durumu üzerindeki etkilerini tanımlamayı amaçladık.

Gereç ve Yöntem: Two hundred seventeen Hodgkin lenfoma hastası ve 205 sağlıklı bireyin trombosit ile ilgili parameterleri incelendi ve karşılaştırıldı. Hastaların değerleri tanı, evre ve nüks durumuna göre karşılaştırıldı. Alım çalışma karakteristik eğrisi analizi ile tanı, evre ve nüks durumu için parameterlerin cutoff değerlerini tanımlamayı planladık.

Bulgular: MPV, Plt ve PCT'nin tanıda kesim değeri sırasıyla 8,49fL, 32.1000/mm^3, 0,31 idi. MPV ve Plt'nin de evrelemede cutoff değeri sırasıyla 9,5fL, 12fL bulundu. Hiçbir parameter nüks ile ilişkili bulunmadı.

Sonuç: Bu, Hodgkin lenfomada trombosit ile ilişkili parameterleri değerlendiren ilk çalışmadır. Sağkalım analizlerini içeren ileri çalışmalar, bu parameterlerin Hodgkin lenfoma üzerindeki etkisini netleştirecektir.

Anahtar Kelimeler: Hodgkin lenfoma, platelet, MPV, PCT, PDW

Address for Correspondence: Aydan Akdeniz, Mersin University Faculty of Medicine, Department of Hematology, Mersin, Turkey
Phone: +90 532 157 8087 E-mail: akdenizdr@hotmail.com ORCID ID: orcid.org/0000-0002-5160-4803

Cite as: Akdeniz A, Mehtap Ö, Karakuş V, Ünal S, Aygün K, Örekici Temel G, Tombak A, Tiftik EN. Are Platelet-related Parameters Predictive of the Prognosis of Hodgkin's Lymphoma? Med J Bakirkoy 2021;17:367-374

Received: 15.09.2021
Accepted: 09.12.2021

INTRODUCTION

Hodgkin's lymphoma (HL) is malignant lymphoid neoplasia with symptoms such as lymphadenopathy, constitutional symptoms, itching, and fatigue upon diagnosis that histologically presents as Reed-Sternberg/Hodgkin cells in the center surrounded by non-neoplastic inflammatory cells. HL has two subtypes: the classical type that constitutes 90% of the cases, and the nodular lymphocyte predominant type that constitutes 10% of the cases. While the classical type has two peak periods, as young adults and older adults, the nodular lymphocyte predominant type is more common in children and in adults in their 40s and 50s (1,2). They are staged according to the Lugano classification, and the treatment is planned according to their early/advanced stage and risk status. Old age, advanced stage, high erythrocyte sedimentation rate, B symptoms, high number of involved lymph nodes, presence of bulky or mediastinal mass, male sex, and leukocytosis (>15,000/mm^3), and lymphopenia (<8% of leukocyte count or absolute lymphocyte count <600/mm^3) are poor prognostic criteria. The treatment is usually curative, and 5-year survival of ≥90% is observed. Response to treatment is usually assessed by imaging methods based on the reduction in tumor mass. However, the prognosis is poor in primary refractory or early relapsed cases. Therefore, in these patients, it is necessary to consider autologous bone marrow transplantation after salvage chemotherapy (3).

Platelets (Plt) are activated by thrombin released by the tumor, and they contribute to tumor formation and propagation by causing the release of angiogenic factors such as Plt-derived growth factor and vascular endothelial growth factor (4). In addition, activated Plts protect tumor cells from lysis (5). Plt-related factors present the characteristic properties (size and activity) of Plts, namely, mean Plt volume (MPV), Plt distribution width (PDW), and plateletcrit (PCT). These parameters are thought to be related to tumor metastases and therefore have predictive value in the prognosis of many tumors such as colon, lung, cervical, and gastric cancers and diffuse large B-cell lymphomas (6-9). Sabrkhany reported that Plt-related parameters could be used in the early diagnosis of early-stage cancer, and in their meta-analyses, Zhang showed that high Plt counts were associated with a poor prognosis in lung cancers (10,11). In another study, Plt >400,000/mm^3 was reported to be a prognostic indicator (12). Conversely, Lopes et al. (13) reported that high pretreatment Plt counts had no predictive value.

MPV refers to the Plt volume and is an early marker of Plt activation. Since MPV decreases as a result of the consumption of large Plts in inflammatory events, it is considered an inflammatory marker. In addition, MPV has been reported to be elevated in myocardial infarction, unstable angina, and stroke (14). This result is probably related to the fact that large Plts cause acute coronary syndrome more frequently. By contrast, in a meta-analysis of 38 studies, Chen et al. (15) reported that MPV had no prognostic value in malignancies. Another study showed that a low MPV reduced overall survival in multiple myeloma (16).

PCT is calculated using the formula MPV × PLT/10 and represents the total Plt volume. Its poor prognostic effect was reported in pancreatic cancers (17). In another study, the PCT value was found to be higher in patients with metastatic lung cancer than in those without metastasis (18).

PDW shows the variation in Plt size. Its increase indicates intense active thrombocyte production. Unlike other Plt-related parameters, the current literature data reveal conflicting results about its prognostic value in solid cancers. Some studies have declared that it is a prognostic factor and plays a role in metastasis, while some have denied these theories (19,20). Hirahara et al. (21) reported no relationship between prognosis and PDW in esophageal cancers.

To the best of our current knowledge, no study has compared Plt-related parameters in healthy populations with patients with HL. Thus, this study aimed to understand whether Plt-related parameters in HL are different from those in healthy populations and affect staging and relapsing status in HL.

METHODS

Local Ethics Committee Approval was obtained from Mersin University (no. 2020/42). Records of 217 patients (aged 18-70 years) histopathologically diagnosed with HL in three centers between January 2000 and December 2020 were retrospectively examined. Demographic data, histological subtypes, stages, MPV, PCT, PDW, and Plt valuesof all patients at the time of diagnosis were recorded. Data of 205 Plt donors who applied to the apheresis unit in one of these centers and were identified as the control (healthy) group and had no malignancy or inflammatory disease at the same interval were also documented. The Chi-squared test was used to examine whether Plt-related factors differ between the patient and control groups, and the Kaplan-Meier method was used to examine whether Plt-related factors were effective on prognosis. We also tried to define the cutoff values of the parameters for diagnosis, stage, and relapsing status using receiving operating characteristic (ROC) curve analysis.

RESULTS

Data of 205 individuals in the control group and 217 patients in the HL group were documented. The mean ages between the two groups were comparable (36.7 and 38.9 years, respectively). Male predominance was more common in both the control and HL groups (95.6% and 64.5%, respectively). The median follow-up time was 58 months. The adriamycin + bleomycin + vinblastine + dacarbazine protocol was the most used treatment protocol (n=118). Overall, histopathological data of 184 patients were obtained. The most common histopathological type was a nodular sclerosing type (n=86). Other types were mixed cellular form (n=67), lymphocyte-rich (n=21), HL + non-HL (n=5), and not otherwise specifed (n=5). Information about the disease stage could be obtained in 185 patients, of which 68 were in the early-stage and 117 were in the advanced stage. The median follow-up time was 68 and 51 months, respectively. Demographic data are summarized in Table 1.

In total, the PDW value was obtained in 54 patients. They were classified according to their staging and relapsing status, except for one patient. The median PDW value was not significantly different in the control and HL groups, early-stage and advanced stage groups, and relapsed and non-relapsed groups (p=0.250, p=0.919, and p=0.936, respectively) (Table 2).

The MPV was significantly higher in the control group than in the HL group (9.7 vs 8.8 fL, p<0.001). It is also higher in the early-stage group than in the advanced stage group (8.9 fL vs 8.4 fL, p=0.033). The mean Plt count was higher in the HL group than in the control group (p<0.001). It was also higher in the advanced stage group than in the early-stage group (p=0.033). While the mean PCT value was lower in the control group than in the HL group, it was not significantly different in patients with early- and advanced stage disease. Values of MPV, Plt, and PCT at the time of diagnosis are summarized in Tables 3,4.

In total, data of 182 patients were evaluated for relapsing status. None of the values of MPV, Plt, and PCT showed a significant difference in terms of relapsing status (Table 5).

Whether the parameters had a diagnostic value was assessed by the ROC curve analysis (Table 6) (Figure 1). Accordingly, the diagnostic cutoff values of MPV and Plt were 8.49 fL and 321,000/mm³, respectively. No significant difference was found between the diagnostic power of MPV and Plt, but both of them were higher than of PCT.

Whether the parameters had a cutoff value for the early and advanced stages were assessed with the ROC curve analysis (Figure 2) (Table 7). The cutoff values of PDW and PCT to determine staging were not defined. To determine advanced disease stages, the cutoff values of MPV and Plt were >9.5 fL and 388,000/mm³, respectively [area under curve (AUC): 0.59, p=0.038 and AUC: 0.60, p=0.0179, respectively]. No difference was found when the predictive power of Plt and MPV values on staging was compared.

Table 1. Demographic data

	HL group	Control group
Number of patients (n)	217	205
Mean age (years)	38.9	36.7
Male/female ratio	64.5	95.6%
Median follow-up time (months)	58	-
Histological subtypes (n)		
nodular sclerosing	86	-
mixed cellular	67	-
lymphocyte-rich	21	-
HL + NHL	5	-
not otherwise specifed	5	-
Stage early	68	-
advanced	117	-

HL: Hodgkin's lymphoma, NHL: Non-Hodgkin's lymphoma

Table 2. Comparison of PDW value between the control and patient groups, early and advanced stage groups, and non-relapsed and relapsed groups

	Control group n=205		HL group n=54		
PDW (fL)	**Median**	**Q1-Q3**	**Median**	**Q1-Q3**	**p**
	12.4	11-16.10	12	10.35-15.55	0.250
	Early-stage n=19		Advanced stage n=34		
PDW (fL)	Median	Q1-Q3	Median	Q1-Q3	p
	13	10-16	12	10.4-15.28	0.919
	Non-relapsed n=44		Relapsed n=7		
PDW (fL)	mean	s. deviation	mean	s. deviation	p
	13.4	5,43923	13,2714	2,85524	0.936

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume, HL: Hodgkin's lymphoma

DISCUSSION

Many studies have shown that Plt-related parameters were prognostic factors and affected overall survival and progression-free survival in many solid-organ cancers and some hematological malignancies such as multiple myeloma

Table 3. Comparison of MPV, Plt, and PCT values between the control and HL groups

	Control group n=205		HL group n=217		
	mean	Standard deviation	mean	Standard deviation	p
MPV(fL)	9.7293	1.16544	8.8432	1.60144	**<0.001**
Plt (1/mm³)	258756.098	43601.6844	319468.203	125302.2311	**<0.001**
PCT	.252585	.0557537	.275647	.1019611	0.004

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume, HL: Hodgkin's lymphoma

Table 4. Comparison of MPV, Plt, and PCT values between the early and advanced stage

	Early-stage n=68		Advanced stage n=117		
	mean	S. deviation	mean	S. deviation	p
MPV(fL)	8.9461	1.66652	8.4364	1.50478	0.033
Plt (1/mm³)	299360.870	114087.6936	341294.068	136682.1025	0.033
PCT	.262196	.0946792	.281737	.1114290	0.224

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume

Table 5. Comparison of MPV, Plt, and PCT values between the non-relapsed and relapsed groups

	Non-relapsed n=148		Relapsed n=34		
	mean	Standard deviation	mean	Standard deviation	p
MPV(fL)	8.7114	1.60248	8.1876	1.38796	0.080
Plt (1/mm³)	321081.757	128370.7466	336602.941	142043.7288	0.534
PCT	.272977	.1045213	.270844	.1136776	0.916

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volume

Table 6. ROC curve analyses for diagnosis

Parameter	AUC (CI)	p	cutoff	Specificity (C)	Specificity (C)
MPV (fL)	0.690 (0.644-0.734)	<0.001	≤8.49	47 (40.2-53.9)	87.80 (82.5-92)
PDW (fL)	0.551 (0.488-0.613)	0.3105	≤10.7	33.96 (21.5-48.3)	88.29 (83.1-92.4)
Plt (1/mm³)	0.653 (0.606-0.699)	<0.001	>321,000	47.47 (40.7-54.3)	90.24 (85.3-93.9)
PCT	0.559 (0.511-0.607)	0.0379	>0.31	34.10 (27.8-40.8)	89.76 (84.8-93.5)

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

and diffuse large B-cell lymphoma. Plts protect tumor cells from lysis, and they are responsible for tumor invasion and metastasis and thrombosis formation by activating nuclear factor-kB and tumor growth factor B/Smad pathways (22,23).

In a previous study, high Plt counts were shown to be associated with a poor prognosis in cancers (24). In the present study, the mean Plt count was higher in patients with HL than in healthy individuals, similar with reports about most cancers. In another study, high Plt counts were shown to be a messenger in early-stage cancers; similarly, it can be speculated that the cutoff Plt count >321,000/mm³ is predictive for the diagnosis of HL (25). Moreover, patients with Plt count >388,000/mm³ was considered to have advanced diseases according to the ROC analysis. Based on this, Plt count >388,000/mm³ can be considered a poor prognostic criterion.

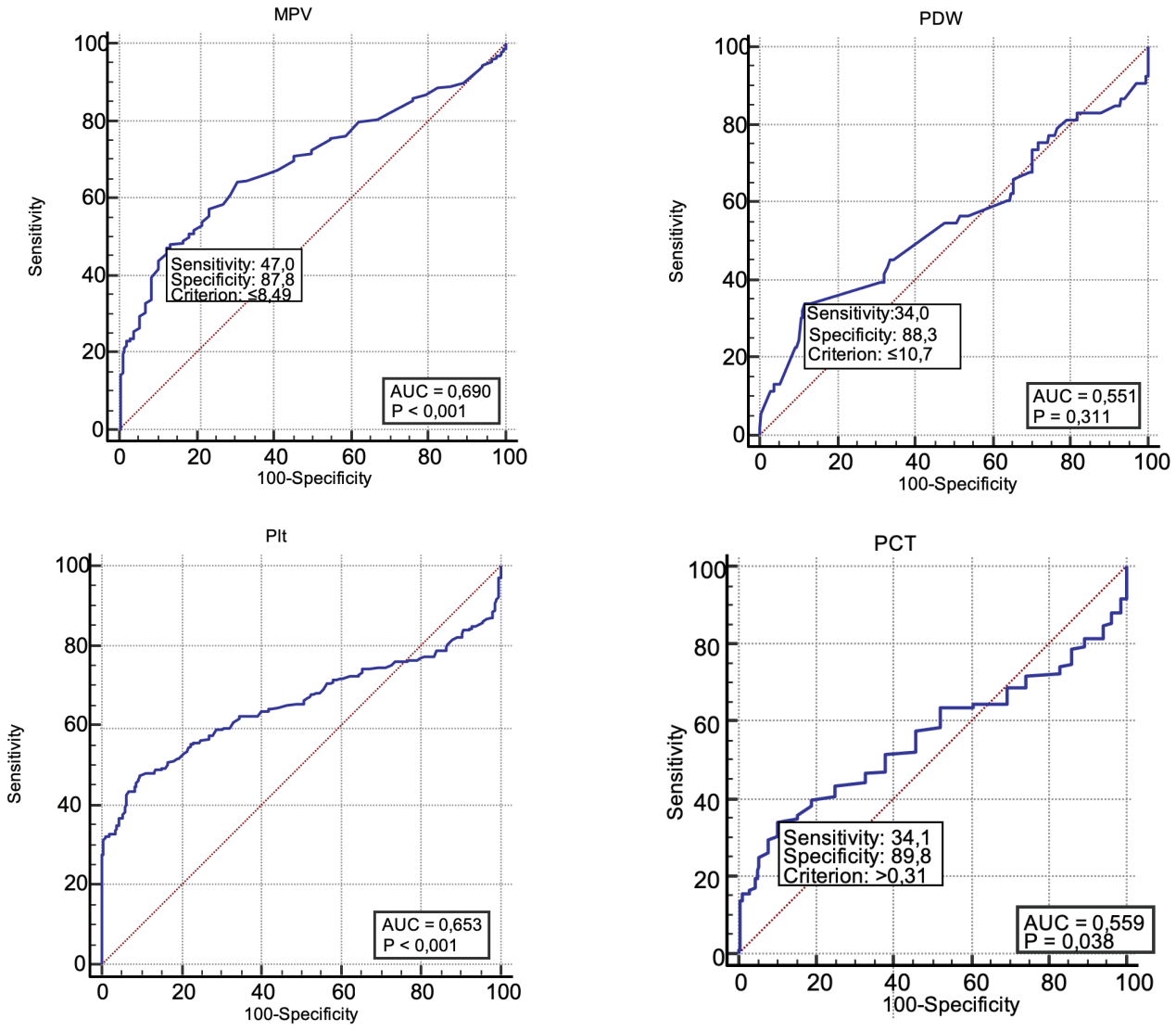

Figure 1. Receiver operating characteristic curve analyses for diagnosis
PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

The MPV value at diagnosis is higher in patients with diabetes mellitus, hypercholesterolemia and metabolic syndrome, and smoking status than in the normal population. High MPV values are associated with atherosclerosis, stroke, and myocardial infarction (26-28). However, the prognosis worsened as the MPV value decreased in patients with cancer. In resectable colon, breast, cervical, renal cell, and lung cancers, diffuse large B-cell lymphoma, and multiple myeloma due to hematological malignancies, low MPV values have been associated with a poor prognosis (6-8, 29-32). In chronic lymphocytic leukemia, those with low MPV values received treatment more frequently and needed initial treatment earlier, with the coexistence of other poor prognostic factors (33). However, MPV was reported to have no prognostic value in malignancies in a meta-analysis (15). In our study, MPV was significantly lower in the HL group than in the control group (8.8 fL vs 9.7 fL), in line with literature data. It was also significantly lower in advanced stage than in early-stage cases (8.4 fL vs 8.9 fL). The diagnostic value of MPV was determined as ≤ 8.49 fL, which was lower than those in the studies for CLL (10.4 fL) and DBBHL (9.1 fL), but similar to that in multiple myeloma (8.5 fL) (9,16, 33). For staging, the cutoff value of MPV was 9.5 fL. Therefore, MPV <9.5 fL may be associated with a poor prognosis. By contrast, MPV was not a strong indicator of relapse.

PCT was reported to have a poor prognostic value in pancreatic and resectable lung cancers and was higher in

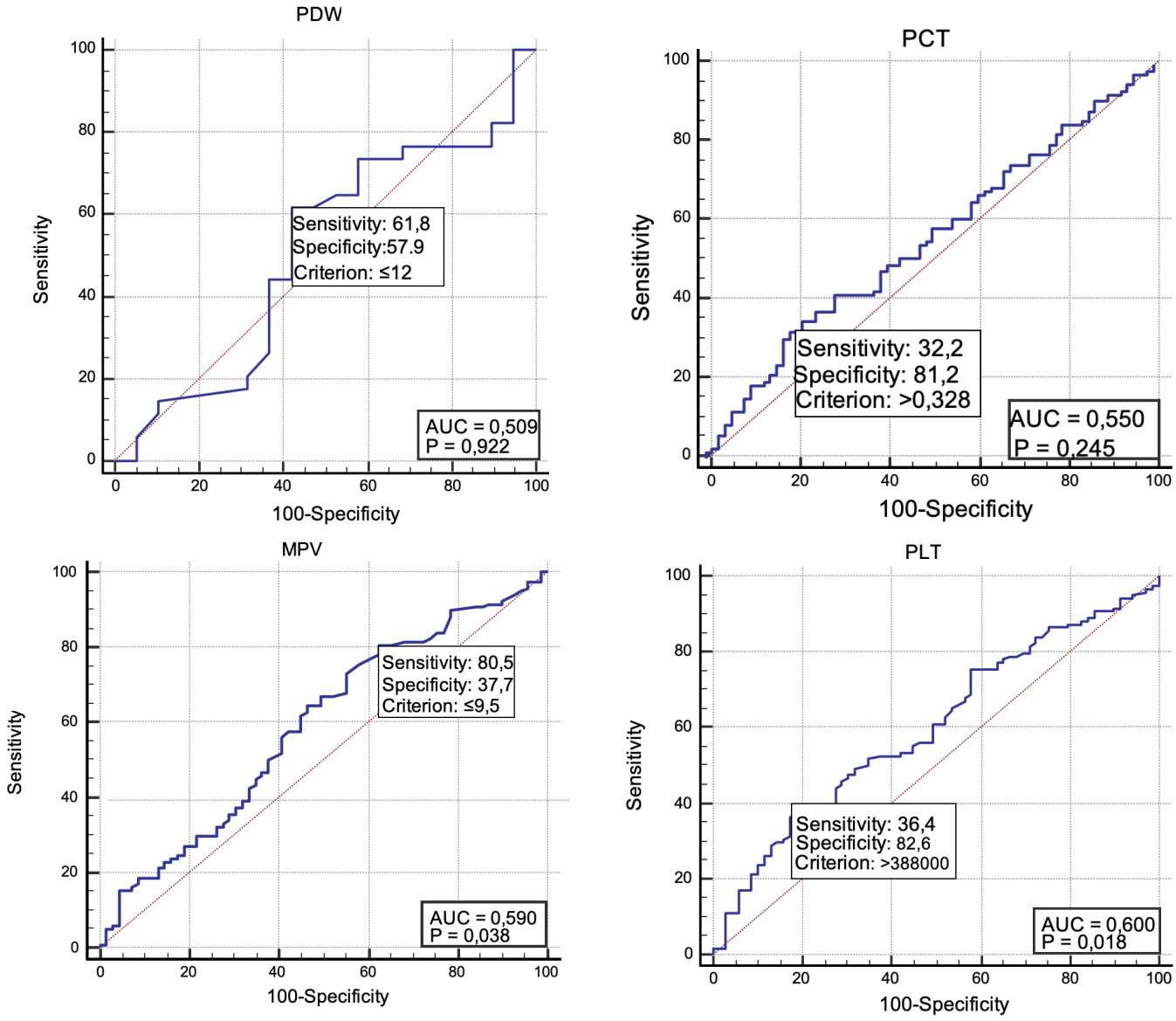

Figure 2. Receiver operating characteristic curve analyses for staging
PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

Table 7. ROC curve analyses for staging

Parameter	AUC (CI)	p	cutoff	Sensitivity (CI)	Specificity (CI)
MPV (fL)	0.590 (0.516-0.662)	0.0380	≤9.5	80.51 (72.2-87.2)	37.68 (26.3-50.2)
PDW (fL)	0.509 (0.368-0.649)	0.9222	≤12	61.76 (43.6-77.8)	57.89 (33.5-79.7)
Plt (1/mm³)	0.600 (0.526-0.671)	0.0179	>388,000	36.44 (27.8-45.8)	82.61 (71.6-90.7)
PCT	0.550 (0.476-0.623)	0.2453	>0.328	15.25 (9.3-23)	89.86 (80.2-95.8)

PDW: Platelet distribution width, PCT: Plateletcrit, MPV: Mean platelet volüme, ROC: Receiver operating characteristic, AUC: Area under curve, CI: Confidence interval

patients with metastatic lung cancer than in those without metastatic ones (6,17,18). In this study, the PCT value was significantly higher in the HL group than in the control group. The cutoff PCT value was identified for diagnosis, but not for staging and relapsing status. Therefore, we could not consider PCT as a prognostic factor for HL.

Current literature data examining the prognostic value of PDW in solid cancers provide conflicting results (19-21). In the present study, no significant difference was found between the HL and control groups and between the early and advanced stages. Thus, PDW may not be a marker of either diagnosis or prognosis.

In this study, we found that PLT, MPV, and PCT have diagnostic values for HL. When the determinative powers of these parameters were compared, no significant difference was found. By contrast, Plt and MPV were found to have a strong effect, but PDW and PCT did not affect staging. When the determinative powers of Plt and MPV were compared, no significant difference was found.

Study Limitations

This study has some limitations. First, the relation of Plt-related factors with survival was not analyzed, and their prognostic values were evaluated based on the stage. Second, because the follow-up times of patients were very short and we could not perform survival analysis, we avoid defining the cutoff values for Plt-related parameters to determine relapsing status. Third, we could not reach the full data of all patients. Fourth, examining the relationships between Plt-related factors and other prognostic factors such as erythrocyte sedimentation rate, B symptoms, number of involved lymph nodes, presence of large mass, presence of mediastinal mass, gender, leukocytosis, and lymphopenia could have strengthened our study.

CONCLUSION

Following our literature reviews, our study is the first to evaluate the comparison of Plt-related parameters in patients with HL and healthy populations. As mentioned above, when examined together with the survival analysis and other variables, the prognostic value of these parameters will become more evident.

ETHICS

Ethics Committee Approval: Local Ethics Committee Approval was obtained from Mersin University (no. 2020/42).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: A.A., Ö.M., V.K., S.Ü., K.A., Concept: Ö.M., V.K., Design: AA., V.K., G.Ö.T., A.T., E.N.T., Data Collection or Processing: A.A., Ö.M., V.K., S.Ü., K.A., Analysis or Interpretation: G.Ö.T., A.T., E.N.T., Literature Search: A.A., V.K., E.N.T., Writing: AA., V.K., E.N.T.

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. Quintanilla-Martinez L. The 2016 updated WHO classification of lymphoid neoplasias. Hematol Oncol 2017;35 Suppl 1:37-45.
2. Shanbhag S, Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. CA Cancer J Clin 2018;68:116-32.
3. Gallamini A, Hutchings M, Ramadan S. Clinical presentation and staging of Hodgkin lymphoma. Semin Hematol 2016;53:148-54.
4. Yuan L, Liu X. Platelets are associated with xenograft tumor growth and the clinical malignancy of ovarian cancer through an angiogenesis-dependent mechanism. Mol Med Rep 2015;11:2449-58.
5. Ferrone C, Dranoff G. Dual roles for immunity in gastrointestinal cancers. J Clin Oncol 2010;28:4045-51.
6. Wang JJ, Wang YL, Ge XX, Xu MD, Chen K, Wu MY, et al. Prognostic Values of Platelet-Associated Indicators in Resectable Lung Cancers. Technol Cancer Res Treat 2019;18:1533033819837261.
7. Wang JM, Wang Y, Huang YQ, Wang H, Zhu J, Shi JP, et al. Prognostic Values of Platelet-Associated Indicators in Resectable Cervical Cancer. Dose Response 2019;17:1559325819874199.
8. Lian L, Xia YY, Zhou C, Shen XM, Li XL, Han SG, et al. Mean platelet volume predicts chemotherapy response and prognosis in patients with unresectable gastric cancer. Oncol Lett 2015;10:3419-24.
9. Zhou S, Ma Y, Shi Y, Tang L, Zheng Z, Fang F, et al. Mean platelet volume predicts prognosis in patients with diffuse large B-cell lymphoma. Hematol Oncol 2018;36:104-9.
10. Sabrkhany S, Kuijpers MJE, van Kuijk SMJ, Sanders L, Pineda S, Olde Damink SWM, et al. A combination of platelet features allows detection of early-stage cancer. Eur J Cancer 2017;80:5-13.
11. Zhang X, Ran Y. Prognostic role of elevated platelet count in patients with lung cancer: a systematic review and meta-analysis. Int J Clin Exp Med 2015;8:5379-87.
12. Chotsampancharoen T, Chavananon S, Sripornsawan P, Duangchu S, McNeil E. Outcome and Prognostic Factors of Childhood Hodgkin Disease: Experience From a Single Tertiary Center in Thailand. J Pediatr Hematol Oncol 2021;43:e85-9.
13. Lopes A, Daras V, Cross PA, Robertson G, Beynon G, Monaghan JM. Thrombocytosis as a prognostic factor in women with cervical cancer. Cancer 1994;74:90-2.
14. Sansanayudh N, Anothaisintawee T, Muntham D, McEvoy M, Attia J, Thakkinstian A. Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. Int J Cardiol 2014;175:433-40.
15. Chen X, Li J, Zhang X, Liu Y, Wu J, Li Y, et al. Prognostic and clinicopathological significance of pretreatment mean platelet volume in cancer: a meta-analysis. BMJ Open 2020;10:e037614.
16. Zhuang Q, Xiang L, Xu H, Fang F, Xing C, Liang B, et al. The independent association of mean platelet volume with overall survival in multiple myeloma. Oncotarget 2016;7:62640-6.
17. Wang L, Sheng L, Liu P. The independent association of platelet parameters with overall survival in pancreatic adenocarcinoma receiving intensity-modulated radiation therapy. Int J Clin Exp Med 2015;8:21215-21.
18. Oncel M, Kiyici A, Oncel M, Sunam GS, Sahin E, Adam B. Evaluation of Platelet Indices in Lung Cancer Patients. Asian Pac J Cancer Prev 2015;16:7599-602.
19. Gunaldi M, Erdem D, Goksu S, Gunduz S, Okuturlar Y, Tiken E, et al. Platelet Distribution Width as a Predictor of Metastasis in Gastric Cancer Patients. J Gastrointest Cancer 2017;48:341-6.

20. Kurtoglu E, Kokcu A, Celik H, Sari S, Tosun M. Platelet Indices May be Useful in Discrimination of Benign and Malign Endometrial Lesions, and Early and Advanced Stage Endometrial Cancer. Asian Pac J Cancer Prev 2015;16:5397-400.
21. Hirahara N, Matsubara T, Kawahara D, Mizota Y, Ishibashi S, Tajima Y. Prognostic value of hematological parameters in patients undergoing esophagectomy for esophageal squamous cell carcinoma. Int J Clin Oncol 2016;21:909-19.
22. Buergy D, Wenz F, Groden C, Brockmann MA. Tumor-platelet interaction in solid tumors. Int J Cancer 2012;130:2747-60.
23. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123-34.
24. Zhang X, Lv Z, Yu H, Zhu J. The clinicopathological and prognostic role of thrombocytosis in patients with cancer: A meta-analysis. Oncol Lett 2017;13:5002-8.
25. Sabrkhany S, Kuijpers MJE, Oude Egbrink MGA, Griffioen AW. Platelets as messengers of early-stage cancer. Cancer Metastasis Rev 2021;40:563-73.
26. Tschoepe D, Roesen P, Esser J, Schwippert B, Nieuwenhuis HK, Kehrel B, et al. Large platelets circulate in an activated state in diabetes mellitus. Semin Thromb Hemost 1991;17:433-8.
27. Nardin M, Verdoia M, Barbieri L, De Luca G; Novara Atherosclerosis Study Group (NAS). Impact of metabolic syndrome on mean platelet volume and its relationship with coronary artery disease. Platelets 2019;30:615-23.
28. Kiliçli-Camur N, Demirtunç R, Konuralp C, Eskiser A, Başaran Y. Could mean platelet volume be a predictive marker for acute myocardial infarction? Med Sci Monit 2005;11:CR387-92.
29. Kumagai S, Tokuno J, Ueda Y, Marumo S, Shoji T, Nishimura T, et al. Prognostic significance of preoperative mean platelet volume in resected non-small-cell lung cancer. Mol Clin Oncol 2015;3:197-201.
30. Yun ZY, Zhang X, Liu ZP, Liu T, Wang RT, Chen H. Association of decreased mean platelet volume with renal cell carcinoma. Int J Clin Oncol 2017;22:1076-80.
31. Seles M, Posch F, Pichler GP, Gary T, Pummer K, Zigeuner R, et al. Blood Platelet Volume Represents a Novel Prognostic Factor in Patients with Nonmetastatic Renal Cell Carcinoma and Improves the Predictive Ability of Established Prognostic Scores. J Urol 2017;198:1247-52.
32. Scheiner B, Kirstein M, Popp S, Hucke F, Bota S, Rohr-Udilova N, et al. Association of Platelet Count and Mean Platelet Volume with Overall Survival in Patients with Cirrhosis and Unresectable Hepatocellular Carcinoma. Liver Cancer 2019;8:203-17.
33. Masternak M, Puła B, Knap J, Waszczuk-Gajda A, Drozd-Sokołowska J, Wdowiak K, et al. Mean Platelet Volume Has Prognostic Value in Chronic Lymphocytic Leukemia. Cancer Manag Res 2020;12:9977-85.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:375-385
DOI: 10.4274/BMJ.galenos.2021.46338

Research

Psychosocial Adjustment of Healthcare Professionals During the COVID-19 Pandemic: Resident Doctors, Nurses, and Caregivers Need Extra Attention

Sağlık Çalışanlarının COVID-19 Pandemi Sürecindeki Psikososyal Uyumları: Asistan Doktorlar, Hemşireler ve Hasta Bakıcıların Ekstra İlgiye İhtiyacı Var

Fatma Akyüz Karacan[1], Semra Yılmaz[2], İsmet Kırpınar[1]

[1]Bezmialem Vakıf University Faculty of Medicine, Department of Psychiatry, Istanbul, Turkey
[2]University of Health Science Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Child Psychiatry Policlinic, Istanbul, Turkey

ABSTRACT

Objective: This study aimed to examine the psychosocial adjustment and its association with occupation, hospital unit, social support, and Coronavirus disease-2019 (COVID-19) attitude in the healthcare professionals during the COVID-19 pandemic.

Methods: This descriptive cross-sectional study was conducted in two pandemic hospitals with a total of 557 participants, which included healthcare professionals of all occupations and all hospital units. Socio-demographic characteristics and COVID-19 attitude and knowledge were evaluated with the data form. The hospital anxiety-depression scale (HADS), beck hopelessness scale (BHS), maslach burnout inventory (MBI), fear of COVID-19 scale (FC-19S), and multidimensional scale of perceived social support (MSPSS) were used to assess psychosocial adjustment and social support.

Results: Females had higher levels of HADS-anxiety, FC-19S, MBI-emotional exhaustion, and MSPSS-friend and MSPSS-significant other subscales ($p<0.05$). Scores of BHS (highest in resident doctors and caregivers), HADS-anxiety (highest in resident doctor), HADS-depression (highest in caregivers), and MBI-emotional exhaustion and MBI-depersonalization (highest in the resident doctors) were seen to differ with occupation ($p<0.05$). Scores of HADS-Depression, FC-19S, and MBI-emotional exhaustion were higher in participants working at the intensive care unit ($p<0.05$). Having COVID-19 polymerase chain reaction examination history was related to higher scores of BHS, HADS-anxiety, HADS-depression, and FC-19S, and lower scores of MSPSS scores ($p<0.05$). MSPSS scores were negatively correlated with HADS-anxiety, HADS-depression, MBI-emotional exhaustion, and MBI-depersonalization scores.

Conclusion: Results indicate that gender, occupation, and hospital unit influence the psychosocial adjustment of healthcare professionals. Moreover, social support, COVID-19 attitude, and psychosocial adjustment are interrelated with each other.

Keywords: Psychosocial adjustment, COVID-19, healthcare professionals, social support, COVID-19 attitude

ÖZ

Amaç: Bu çalışmada Koronavirüs hastalığı-2019 (COVID-19) pandemi sürecinde sağlık çalışanlarının psikososyal uyumu ile meslek, hastane çalışma birimi, sosyal destek ve COVID-19 tutumu arasındaki ilişkinin incelemesini amaçladık.

Gereç ve Yöntem: Kesitsel ve tanımlayıcı olan bu çalışma 2 pandemi hastanesinde yürütüldü. Katılımcılar, tüm meslek guruplarından ve tüm hastane çalışma birimlerinden alınan toplam 557 sağlık çalışanı idi. Sosyo-demografik özellikler ile COVID-19 tutum ve bilgi düzeyini değerlendirmek için araştırmacılar tarafından geliştirilmiş veri formu kullanıldı. Psikososyal uyum ve sosyal desteğin değerlendirilmesi için; Hastane anksiyete-depresyon ölçeği (HADÖ), beck umutsuzluk ölçeği (BUÖ), maslach tükenmişlik ölçeği (MTÖ), COVID-19 korkusu ölçeği ve çok boyutlu algılanan sosyal destek ölçeği (ÇBASDÖ) kullanıldı.

Bulgular: HADÖ-anksiyete, COVID-19 korkusu ölçeği, MTÖ-duygusal tükenme, ÇBASDÖ-arkadaş ve özel arkadaş alt ölçek puanları kadınlarda erkeklere göre daha yüksekti ($p<0,05$). BUÖ (en yüksek asistan doktorlarda ve hasta bakıcılarda), HADÖ-anksiyete (asistan doktorlarda en yüksek), HADÖ-depresyon (hasta bakıcılarda en yüksek), MTÖ-duygusal tükenme ve duyarsızlaşma (asistan doktorlarda en yüksek) puanları olarak görüldü ve mesleğe göre farklılık göstermekteydi ($p<0,05$). COVID-19 polimeraz zincirleme reaksiyonu testi yaptırmayanlarla kıyaslandıklarında,

Address for Correspondence: Fatma Akyüz Karacan, Bezmialem Vakıf University Faculty of Medicine, Department of Psychiatry, Istanbul, Turkey
Phone: +90 212 453 17 00 E-mail: ftmakyuz@yahoo.com.tr ORCID ID: orcid.org/0000-0001-6166-9355

Cite as: Akyüz Karacan F, Yılmaz S, Kırpınar İ. Psychosocial Adjustment of Healthcare Professionals During the COVID-19 Pandemic: Resident Doctors, Nurses, and Caregivers Need Extra Attention. Med J Bakirkoy 2021;17:375-385

Received: 13.09.2021
Accepted: 25.10.2021

yaptıranlarda BUÖ, HADÖ-anksiyete, HADÖ-depresyon, COVID-19 korkusu puanları daha yüksek ve ÇBASDÖ puanları daha düşüktü (p<0,05). ÇBASDÖ puanları ile HADÖ-anksiyete, HADÖ-depresyon, MTÖ-duygusal tükenme ve MTÖ-duyarsızlaşma puanları arasında negatif korelasyon vardı.

Sonuç: Çalışmamızın sonuçları sağlık çalışanlarının psikososyal uyumunun cinsiyet, meslek ve hastane çalışma biriminden etkilendiğini göstermiştir. Ayrıca sosyal destek, COVID-19 tutumu ve psikososyal uyum birbiriyle ilişkilidir.

Anahtar Kelimeler: Psikososyal uyum, COVID-19, sağlık çalışanları, sosyal destek, COVID-19 tutum

INTRODUCTION

Pandemic refers to the occurrence of a specific disease worldwide or over a very wide area that crosses international boundaries, which usually affects a large number of people (1). Coronavirus disease-2019 (COVID-19) was first seen in China in December 2019, which quickly became a worldwide threat, and was declared a pandemic by the World Health Organization in March 2020. The first case in Turkey was reported on March 11, 2020, and as of April 30, 2021, the total number of reported cases was 4,820,591 with 40,131 deaths (2). It has been approximately 1.5 years since the pandemic started. Important progress has been achieved in its treatment during this period; however, the exact treatment is yet to be found.

Isolation is the most effective method in the primary treatment of infectious diseases (3). Therefore, together with face masks and hand hygiene, it has been the main measure that was used to prevent the spread of the disease during the COVID-19 pandemic (4). Since the disease has a very high transmission rate and many people showed to be asymptomatic carriers of the virus, the governments had to enforce strict social isolation rules that must be followed by all people, regardless of their health status. Similar to many countries, several precautions were taken for social isolation in Turkey since the pandemic began. The national and international transportations were restricted and even prohibited, and shopping malls and entertainment centers were closed and education was switched to online applications. The time for these restrictions and regulations to return to the past normal is still unknown. Pandemics can cause social changes, regulations, and restrictions, along with many uncertainties. Moreover, everyone is affected by these changes in their daily lives and work habits, and problems in food, shelter, and basic needs arise, aside from the direct effect of the disease during this pandemic. All these situations may lead to increased psychosocial distress in individuals.

Studies have demonstrated that public mental health is adversely affected during the COVID-19 pandemic (5,6). Healthcare professionals, occupying the frontline during pandemics, have increased risk for mental health besides the increased risk of contacting viral infection (7-9). Excessive workload, unpreparedness, and emotional distress are the reported reasons for increased psychological problems in the health professionals (e.g., fear of infection and family concerns) (4,8). Compared to previous ones, the COVID-19 pandemic is more challenging because of some specific features of the virus, such as high contagiousness, a rather low level of knowledge on its course and long-term consequences, and a lack of established treatments or vaccines (10). Moreover, this is an unprecedented scenario for most hospitals worldwide, which is accompanied by great challenges in various aspects of health care, such as hygiene concepts, sufficient protective measures and equipment, and competence and capacity of the intensive care unit (ICU). Furthermore, many healthcare professionals have been isolated, not only from their social environment but also from their families unlike other people because of their higher risk of contacting the virus and becoming a carrier and their exposure to the illness and loss of their counterparts.

Studies demonstrated that healthcare professionals have higher levels of anxiety and hopelessness compared to the community samples during the COVID-19 pandemic (4). Symptoms of anxiety, depression, stress, and burnout are more common in frontline healthcare professionals, who are involved in the diagnosis, treatment, and care of patients with COVID-19, compared to those who do not work on the frontline (11,12). Gender and occupation showed the importance for their psychological well-being; fear of COVID-19 is higher in females and nurses (13). Social support is associated with a positive COVID-19 attitude in health professionals (14). Social support was associated with burnout in nurses who are at the center of this pandemic (15). Many studies were conducted on healthcare professionals; however, they were carried out especially in the acute and shock phase of the pandemic and examined only certain symptoms by considering limited parameters.

Therefore, this study aimed to examine the psychological adjustment and its association with COVID-19 attitude and social support among the frontline healthcare professionals during the COVID-19 pandemic in Turkey. The study was conducted 8 weeks after the emergence of the pandemic

to eliminate the acute stress effects. Out first hypothesis is that anxiety, depression, burnout, and hopelessness would be higher in healthcare professionals who had more contact with patients with COVID-19. The second is that higher social support and a positive attitude towards COVID-19 would be associated with better psychological adaptation.

METHODS

Study Design and Participants

This descriptive cross-sectional study was conducted from May 1, 2020, to June 30, 2020, in two state hospitals that were located on the European side of Istanbul. These two hospitals share the same staff and serve most of the COVID-19 cases on the European side of Istanbul since the beginning of the COVID-19 pandemic. The total number of hospital beds of these hospitals is 1,618 (1,008+610) and the total intensive care beds are 513 (408+105). Assuming a pooled standard deviation of 5 units, the study would require a sample size of 44 for each group (i.e., a total sample size of 88, assuming equal group sizes) to achieve a power of 80% and a significance level of 5% (two-sided) and detect a true difference in means between the test and the reference group of 3 units. Inclusion criteria of the study include healthcare professionals who are 18-65 years old, with voluntary participation in the study and are capable of filling up the forms. Healthcare professionals were asked about their medical and psychiatric history, and those with a psychiatric or chronic illness were excluded from the study. Participants were divided into 6 subgroups according to their occupations: specialist doctors, resident doctors, nurses, caregivers, medical secretaries, and security guards. All participants filled out the data form, hospital anxiety-depression scale (HADS), beck hopelessness scale (BHS), maslach burnout scale, fear of COVID-19 scale (FC-19S), and multidimensional scale of perceived social support (MSPSS).

Measurements Tools

Data form: This form was developed by the researchers to gather information related to sociodemographic information (e.g., sex, age, family, and occupation) and COVID-19 attitudes and knowledge of participants. Questions related to COVID-19 attitudes and knowledge were as follows: 1) Are you following new literature knowledge on COVID-19 disease? (answers were: 1. yes and 2. no); 2) Did you have laboratory, radiological, and COVID-19 polymerase chain reaction (PCR) tests until today? (answers were: 1. yes and 2. no); 3) Do you think the pandemic will end (answers were: 1. yes and 2. no); 4. Do you think your institution provides adequate protection methods for COVID-19? (answers were: 1. yes, 2. no, and 3. partially provided).

HADS: This is a 4-point scale consisting of two subscales, HADS-anxiety (rating the anxiety level) and HADS-depression (rating the depression level). Each subscale consists of seven items. Participants answer each item thinking of their emotions and/or behavior during the past week. Higher scores indicate higher levels of anxiety and depression (16). The Turkish validity and reliability study was done by Aydemir et al. (17).

BHS: This is a 20 item self-assessment instrument to measure hopelessness (18). The participant is asked to evaluate each of the 20 statements and decide whether the statement describes his/her attitude in the previous week. The scale has nine inverse items to prevent acquiescence. The total score range from 0 to 20, indicating the number of items endorsed in the hopeless direction. Its Turkish validity and reliability were done by Durak and Palabıyıkoğlu (19).

Maslach Burnout Inventory (MBI): The MBI is a 7-point Likert-type scale, consisting of a 22-item rating of the three dimensions of burnouts, namely emotional exhaustion, depersonalization, and personal accomplishment (20). Its Turkish validity and reliability study was done by Ergin (21).

FC-19S: It was developed by Ahorsu et al. (22) to measure the fear level related to COVID-19. The 5-point Likert type scale has a single factor structure and consists of seven items (1= strongly disagree; 5= strongly agree) (22). Its Turkish validity and reliability study was done by Ladikli et al. (23).

MSPSS: This Likert-type scale was developed by Zimet et al. (24) which evaluates the adequacy of social support received from three different sources: family (MDSPSS-Family), friends (MDSPSS-Friends), and significant others (MDSPSS-significant others). It has a total of 12 items. Its Turkish validity and reliability study was done by Eker et al. (25).

Ethical Approval

Written and verbal consent of each participant was obtained. This study was conducted according to the provisions of the Declaration of Helsinki in 1995. Approval was obtained from the ethics committee of the same hospital with the University of Health Sciences Turkey, Bakirköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2020-157).

Statistical Analysis

The Number Cruncher Statistical System program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage,

minimum, and maximum) were used to evaluate the study data. The suitability of quantitative data to normal distribution was tested by the Shapiro-Wilk test and graphical analysis. The Student's t-test was used to compare normally distributed quantitative variables between two groups, and the Mann-Whitney U test was used to compare quantitative variables that did not show normal distribution between two groups. The One-Way analysis of variance and Bonferroni corrected binary evaluations were used to compare more than two groups of quantitative variables with normal distribution. The Kruskal-Wallis and Dunn-Bonferroni tests were used to compare more than two groups of quantitative variables that did not show normal distribution. The statistical significance was accepted as $p<0.05$. Relationships between numerical variables were examined with the Pearson Correlation Coefficient. Dunn's test was performed to make pairwise comparisons. P-values of <0.05 were considered statistically significant.

RESULTS

Characteristics of the Sample

A total of 557 healthcare professionals, wherein 204 (36.6%) were male and 353 (63.4%) were female, participated in the study. Among the participants 26.9% (n=150) were specialist doctor, 13.6% (n=76) were resident doctor, 17.4% (n=97) were nurse, 16.5% (n=92) were medical secretary, 14.7% (n=82) were caregiver, and 10.8% (n=60) were security guard. Majority of them was working in outpatient (37.7%; n=210) and inpatients clinics (30.9%; n=172), whereas the rest was working in emergency (16.0%; n=89) and ICU (15.4%; n=86).

Attitudes and COVID-19-related Knowledge of Participants

Among the participants, 67.1% (n=374) had the COVID-19 test and 43.8% (n=244) had the thoracic computerized tomography examination at least once since the pandemic began. The test result was positive in 20.9% (n=78) of those who had the COVID-19 polymerase chain reaction (PCR) test. Sufficient protection for themselves against the COVID-19 infection was thought to be provided by their institutions in 39.9% of participants. The attitudes and COVID-19-related knowledge of Participants' are presented in Table 1.

Gender Differences in Scale Scores

Evaluation of gender differences in scale scores revealed that females had higher levels of HADS-anxiety ($p=0.001$; $p<0.01$), FC-19S ($p=0.001$; $p<0.01$), MBI-emotional exhaustion ($p=0.001$; $p<0.01$), MSPSS-friend ($p=0.018$; $p<0.05$), and MSPSS-significant other subscale ($p=0.017$; $p<0.05$) than males (Figure 1).

Table 1. Attitudes and COVID-19-related knowledge of participants

Keeping track of new literature knowledge about COVID-19	Yes	503 (90.3)
	No	54 (9.7)
COVID-19 PCR examination	Yes	374 (67.1)
	No	183 (32.9)
Thoracic CT examination	Yes	244 (43.8)
	No	313 (56.2)
COVID-19 test result	Positive	78 (20.9)
	Negative	296 (79.1)
Thinking that hospital management provide adequate COVID-19 protection methods for him/herself	Agree	222 (39.9)
	Do not agree	29 (5.2)
	Partially agree	306 (54.9)
Thinking that the pandemic will end	Agree	310 (55.7)
	Do not agree	247 (44.3)

COVID-19: Coronavirus disease-2019, CT: Computerized tomography, PCR: Polymerase chain reaction

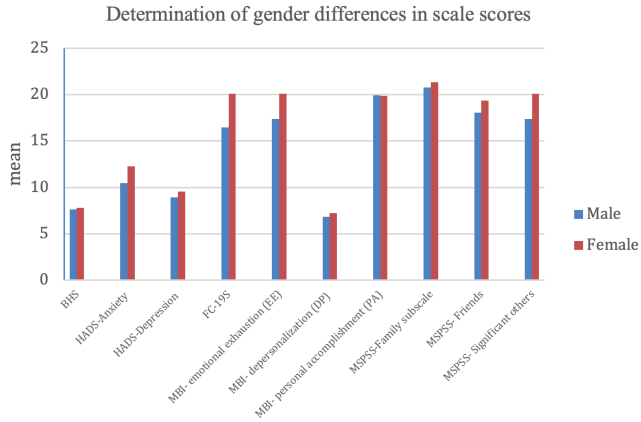

Figure 1. Determination of gender differences in scale scores

Occupational Differences in Scale Scores

The Kruskal-Wallis test and One-Way ANOVA analysis were performed to differentiate the variables into occupational groups, and results were reported in Table 2. No gender difference was found in the FC-19S scores. The BHS scores were significantly higher in resident doctors (mdn=8) and caregivers (mdn=10) compared to other occupational groups [H (5)=45,583, $p<0.001$]. The HADS-anxiety scores were significantly higher in resident doctors [F (5,5511)=3,072, $p=0.011$]and the HADS-depression scores were higher in caregiver [F (5,551)=4,557, $p<0.001$] than the others. The MBI-emotional Exhaustion [F (5,551)=10.094, $p<0.001$] and MBI-Depersonalization [H (5)=29,190, $p<0.001$] scores were highest in the resident doctors than others. The MBI-personal accomplishment scores

Table 2. Determination of occupational differences in scale scores

[1]Caregivers		Occupation of the participant						Test-value (Anova and KW)	p	Post Hoc (Bonferroni/ Dunn test)
		[2]Medical secretary	[3]Security guard	[4]Nurse	[5]Specialist doctor	[6]Resident doctor				
BHS[c]	Min-max (median)	1-20 (10)	1-21 (5)	1-20 (5)	1-17 (5)	1-19 (4)	1-19 (8)	H: 45.583	<0.001**	2-4-5<1-6 3<1
	Mean ± SD	10.22±5.73	7.43±5.33	7.35±5.54	7.27±5.26	6.03±4.79	9.62±5.27	-	-	
HADS-anxiety[d]	Min-max (median)	4-21 (9.5)	6-18 (11)	5-20 (10.5)	5-19 (11)	4-21 (11)	6-21 (14)	F: 3.072	0.011*	2-3<6
	Mean ± SD	11.98±5.34	11.13±3.48	10.4±4.33	11.48±4.18	11.5±4.63	13.01±4.16	-	-	
HADS-depression[d]	Min-max (median)	5-21 (10)	2-19 (8)	2-19 (7)	4-18 (8)	4-20 (8)	5-17 (8)	F: 4.557	<0.001**	2-3-4-5-6<1
	Mean ± SD	11.67±5.14	9.05±3.88	8.63±4.7	9.38±3.69	8.65±3.99	9.12±3.52	-	-	
FC-19S[d]	Min-max (median)	7-35 (20)	7-34 (18.5)	7-35 (20)	7-33 (19)	7-35 (17)	7-33 (18)	F: 1.624	0.155	-
	Mean ± SD	19.99±7.16	19.28±7.75	19.82±7.89	18.56±6.68	17.67±6.59	18.49±5.21	-	-	
MBI-emotional exhaustion[d]	Min-max (median)	5-36 (18)	7-35 (21.5)	4-35 (16)	6-34 (19)	5-36 (19)	12-38 (22)	F: 10.094	<0.001**	1-2-3-4-5<6
	Mean ± SD	17.21±9.53	19.64±7.29	16.1±9.12	18.84±8.08	18.61±6.92	24.24±6.99	-	-	
MBI- depersonalization[c]	Min-max (median)	1-17 (7)	1-18 (7)	1-20 (5)	1-18 (5)	1-17 (6)	1-19 (9.5)	H: 29.190	<0.001**	3-4-5<6
	Mean ± SD	7.29±4.64	7.39±4.07	6.3±5.38	6.29±4.68	6.56±4.03	9.18±4.21	-	-	
MBI-personal accomplishment[d]	Min-max (median)	9-29 (17)	9-33 (19)	3-31 (23)	8-30 (20)	12-31 (21.5)	10-25 (19)	F: 11.060	<0.001**	5<1-2-4-6 1-3<6
	Mean ± SD	17.96±4.51	19.1±6.05	21.55±6.81	19.64±5.89	21.67±4.54	18.29±3.83	-	-	
MSPSS-family subscale[c]	Min-max (median)	4-28 (16)	11-28 (24)	7-28 (21.5)	7-28 (21)	8-28 (24)	8-28 (22)	H: 62.031	<0.001**	1<2-3-4-5-6 4-6<5
	Mean ± SD	16.32±7.22	22.55±4.85	21.73±5.84	20.85±5.13	23.17±4.58	20.3±5.7	-	-	
MSPSS-friends[d]	Min-max (median)	4-28 (12)	8-28 (22)	5-28 (20)	4-28 (19)	7-28 (20)	4-28 (20)	F: 15.325	<0.001**	1<2-3-4-5-6
	Mean ± SD	13.98±6.48	20.8±5.67	19.05±6.25	18.69±5.08	20.39±5.99	18.76±5.97	-	-	
MSPSS-significant others[c]	Min-max (median)	4-28 (14)	4-28 (21)	4-28 (16)	4-28 (16)	4-28 (20)	4-28 (16)	H: 31.898	<0.001**	1<2-5 6<2
	Mean ± SD	14.05±6.88	19.73±6.91	17.13±8.59	17.07±7.18	18.1±6.96	16.01±6.95	-	-	

[c]Kruskal-Wallis test, [d]One-Way ANOVA, **p<0.01 BHS: Beck hopelessness scale, HADS: Hospital anxiety and depression scale, FC-19S: Fear of COVID-19 scale, MBI: Maslach burnout inventory, MPSS: Multidimensional scale of perceived social support, COVID-19: Coronavirus disaese-2019, SD: Standart deviation, Min: Minimum, Max: Maximum

were statistically significantly higher in specialist doctors (mdn=21.5) and security guards (mdn=23) compared to others [F (5,551)=11.060, p<0.001]. The MSPSS-family scores were significantly higher in specialist doctors compared to nurses and resident doctors [H (5)=62,031, p<0.001].

Hospital Unit Differences in Scale Scores

The Kruskal-Wallis test and One-Way ANOVA analysis were performed to determine the hospital unit differences in scale scores, and results were presented in Table 3. Compared to those working in other hospital units, participants working at ICU had significantly higher scores of HADS-depression [F (3,553)=6,759, p=0.001], FC-19S [F (3,553)=8,961, p<0.001] and MBI-emotional exhaustion [F (3,553)=5,690, p<0.001]. Compared to those working in inpatient clinics, participants working in outpatient clinics had significantly higher scores of MBI-personal accomplishment [F (3,553)=5,881, p<0.001] and MSPSS-family [H (3)=15,729, p<0.001] and MSPSS-friends [F (3,553)=6,828, p<0.001]. No difference was found in the hospital unit in the BHS, HADS-anxiety, MBI-depersonalization, and MSPSS-significant other scores.

Relationship Between Scale Scores and COVID-19 PCR Testing Status Among Participants

Participants were examined in 2 groups, as those who had the COVID-19 PCR test and those who did not, and the scale scores of these two groups were compared. The Mann-Whitney and Student's t-tests were applied in statistics and results are shown in Table 4. Those who had the COVID-19 PCR test (mdn=6) had a significantly higher BHS score (z=-3.123, p=0.002) than those who did not (mdn=5). Scores of HADS-anxiety (t=3.024, p=0.003), HADS-depression (t=3.382, p=0.001),and FC-19S (t=3.022, p=0.003) were higher among those who had COVID-19 PCR test than those who did not, and the MSPSS-friend average scores were low. The MSPSS-Significant score value was lower in those who had the COVID-19 PCR test (mdn=17.5) than those who did not (mdn=20) (z=-2.222, p=0.026).

Table 3. Determination of hospital unit differences in scale scores

[1]Out-patient clinic		Hospital Unit				Testr value (Anova and KW)	p	Post Hoc (Bonferroni/ Dunn test)
		[2]Emergency unit	[3]Inpatient clinic	[4]ICU				
BHS[c]	Min-max (median)	1-21 (5)	1-20 (6)	1-20 (6)	1-19 (9)	H: 6.807	0.078	-
	Mean ± SD	7.22±5.47	7.69±5.25	7.65±5.26	9.16±5.75	-	-	-
HADS-anxiety[d]	Min-max (median)	5-21 (11)	5-20 (10)	4-21 (11)	4-21 (11.5)	F: 1.189	0.313	-
	Mean ± SD	11.67±4.4	11.7±4.72	11.14±4.3	12.21±4.51	-	-	-
HADS-depression[d]	Min-max (median)	4-20 (8)	2-19 (8)	2-19 (8)	5-21 (9)	F: 6.759	<0.001**	1-2-3<4
	Mean ± SD	8.75±3.74	9.39±4.4	8.99±3.86	11.5±5.22	-	-	
FC-19S[d]	Min-max (median)	7-33 (18)	7-33 (16)	7-35 (17)	7-35 (21)	F: 8.961	<0.001**	1-2-3<4
	Mean ± SD	18.93±6.72	17.67±7.14	17.56±6.58	21.94±6.81	-	-	-
MBI-emotional exhaustion[d]	Min-max (median)	4-38 (19)	5-36 (19)	5-36 (18)	6-37 (21)	F: 5.690	<0.001**	1-2-3<4
	Mean ± SD	19.21±7.73	18±8.96	18.04±7.7	22.16±8.59	-	-	-
MBI-depersonalization[c]	Min-max (median)	1-20 (6)	1-18 (7)	1-19 (7)	1-17 (7)	H: 0.289	0.962	-
	Mean ± SD	7.2±4.61	6.87±4.44	7.16±4.55	6.9±4.32	-	-	-
MBI-personal accomplishment[d]	Min-max (median)	3-30 (21)	8-33 (20)	8-31 (19)	9-28 (18.5)	F: 5.881	<0.001**	3-4<1
	Mean ± SD	20.98±5.48	20.06±5.51	19.03±5.23	18.65±5.19	-	-	-
MSPSS-family subscale[c]	Min-max (median)	8-28 (23)	4-28 (20)	4-28 (21)	4-28 (21)	H: 15.729	<0.001**	2-3-4<1
	Mean ± SD	22.46±4.9	20.33±5.97	20.53±6.4	19.77±6.36	-	-	-
MSPSS-friends[d]	Min-max (median)	6--28 (20)	5-28 (19)	4-28 (18)	4-28 (17)	F: 6.828	<0.001**	3-4<1
	Mean ± SD	20.19±6.06	18.54±6.07	18.4±6.17	16.81±6.48	-	-	-
MSPSS-significant others[c]	Min-max (median)	4-28 (19.5)	4-28 (20)	4-28 (17.5)	4-28 (17)	H: 3.722	0.293	-
	Mean ± SD	17.79±7.41	17.25±8.11	16.9±6.94	16.35±7.14	-	-	-

[c]Kruskal-Wallis test, [d]One-way ANOVA **p<0.01 BHS: Beck hopelessness scale, HADS: Hospital anxiety and depression scale, FC-19S: Fear of COVID-19 scale, MBI: Maslach burnout ınventory, MPSS: Multidimensional scale of perceived social support, SD: Standart deviation, Min: Minimum, Max: Maximum

Table 4. Relationship between the scale scores and COVID-19-PCR testing status among participants

YES		Did the participant have COVID-19 PCR test until now		Test value (U)	p
		NO			
BHS[a]	Min-max (median)	1-21 (6)	1-17 (5)	z: -3.123	0.002**
	Mean ± SD	8.29±5.7	6.57±4.68	-	-
HADS-anxiety[b]	Min-max (median)	4-21 (12)	5-21 (10)	t: 3.024	0.003**
	Mean ± SD	11.96±4.71	10.85±3.73	-	-
HADS-depression[b]	Min-max (median)	2-21 (9)	2-20 (8)	t: 3.382	<0.001**
	Mean ± SD	9.74±4.47	8.55±3.6	-	-
FC-19S[b]	Min-max (median)	7-35 (19)	7-31 (17)	t: 3.022	0.003**
	Mean ± SD	19.34±7.37	17.62±5.68	-	-
MBI-emotional exhaustion[b]	Min-max (median)	4-37 (19)	5-38 (19)	t: -0.360	0.719
	Mean ± SD	19.02±8.37	19.29±7.76	-	-
MBI-depersonalization[a]	Min-max (median)	1-20 (7)	1-18 (6)	z: -0.469	0.639
	Mean ± SD	7.11±4.42	7.05±4.7	-	-
MBI-personal accomplishment[b]	Min-max (median)	8-33 (20)	3-31 (20)	t: -0.475	0.635
	Mean ± SD	19.79±5.25	20.03±5.81	-	-
MSPSS-family[a]	Min-max (median)	4-28 (22)	8-28 (22)	z: -1.565	0.118
	Mean ± SD	20.76±6.16	21.81±5.22	-	-
MSPSS-friends[b]	Min-max (median)	4-28 (19)	8-28 (20)	t: -3.216	<0.001**
	Mean ± SD	18.26±6.47	20.06±5.63	-	-
MSPSS-significant others[a]	Min-max (median)	4-28 (17.5)	4-28 (20)	z: -2.222	0.026*
	Mean ± SD	16.73±7.42	18.18±7.09	-	-

[a]Mann-Whitney U test, [b]Student's t-test, *p<0.05, **p<0.01, BHS: Beck hopelessness scale, HADS: Hospital anxiety and depression scale FC-19S: Fear of COVID-19 scale, MBI: Maslach burnout ınventory, MPSS: Multidimensional scale of perceived social support COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, SD: Standart deviation, Min: Minimum, Max: Maximum

Comparisons of Social Support Subscale (MSPSS) Scores With Other Scale Scores

The Pearson correlation analysis was applied to determine the relationship between the MSPSS scores and other scale scores, and the results are shown in Table 5. Negative correlations were found between the scores of BHS and each MSPSS subscales [Family (r=-0.397), Friend (r=-0.366) and Significant other (r=-0.369)] (for all p<0.01). In addition, the MSPSS (family, friend, and significant other) scores were negatively correlated with HADS-anxiety, HADS-depression, and MBI-emotional exhaustion (p<0.01). A statistically significant negative correlation was found between the MSPSS-friend and FC-19S scores (r=-0.167, p<0.01). Moreover, the MSPSS (family, friend, and significant other) scores positively correlated with MBI- depersonalization (r=0.228, r=0.207, and r=0.242, respectively) (for all, p<0.01).

DISCUSSION

Many people suffered a severe illness course or died due to COVID-19 infection. Many experienced severe illnesses or the death of loved ones. In addition, people were exposed to economical, daily life, educational, and occupational changes. Many governments applied rules for social isolation to both sick and healthy individuals to prevent the spread of the disease. The time to return to previous normals is unknown. All these may lead to increased distress in an individual's life. Recent studies have demonstrated that the COVID-19 pandemic leads to distress and negative outcomes on the psychosocial well-being of the general population. Health workers are also part of society. Moreover, they have to work with patients with COVID-19 due to their professions, which makes it inevitable for them to be affected by the pandemic process. Healthcare professionals carry increased risk not only in physical but also mental health

Table 5. Comparisons of social support subscale scores with other scale scores

		MSPSS-family subscale	MSPSS-friends subscale	MSPSS-significant others subscale
BHS	r	-0.397**	-0.366**	-0.369**
	n	557	557	557
HAD-A	r	-0.235**	-0.214**	-0.194**
	n	557	557	557
HAD-D	r	-0.340**	-0.316**	-0.345**
	n	557	557	557
FC-19S	r	-0.108*	-0.167**	-0.085*
	n	557	557	557
MBI-emotional exhaustion	r	-0.110**	-0.168**	-0.150**
	n	557	557	557
MBI-depersonalization	r	-0.182**	-0.198**	-0.202**
	n	557	557	557
MBI-personal accomplishment	r	0.228**	0.207**	0.242**

BHS: Beck hopelessness scale, HADS: Hospital anxiety and depression scale, FC-19S: Fear of COVID-19 scale, MBI: Maslach burnout ınventory, MPSS: Multidimensional scale of perceived social support

because they work in the frontline during the pandemic (4,7,9). Psychosocial adjustment to a specific stressor is related to the characteristics and social environment of the individual. Therefore, people are not equally influenced by stressor exposure during the pandemic. This study aimed to examine the psychosocial adjustment and its individual and environmental correlation in healthcare professionals who worked in pandemic hospitals from the beginning of the pandemic. That is, we examined the healthcare professionals who worked at the frontline during this pandemic and found that their psychological well-being was related to their gender, occupation, and the hospital unit where they worked during the pandemic. Moreover, social support, COVID-19 attitude, and psychosocial adjustment were interrelated with each other.

Studies have shown that during the COVID-19 pandemic, the psychosocial adjustment of the healthcare professionals is affected by gender, and females have higher anxiety, depression, and distress levels than males (11,12,26). In addition, a systematic review and meta-analysis study in this group have found that the pooled anxiety prevalence was 29.06% in females and 20.92% in males (27). This current study found higher levels of anxiety, COVID-19 fear, emotional exhaustion, and social support in female healthcare professionals compared to male counterparts. The female gender is well-known to be associated with an increased risk for anxiety disorders and is more vulnerable than males in the presence of stress (28). Our gender-related result supports the literature knowledge.

Examination of participants according to their occupational groups and hospital units showed that psychological health was most dramatically affected in assistant doctors, caregivers, and those working in the ICU. The highest levels of anxiety, hopelessness, emotional exhaustion and depersonalization were seen in assistant doctors, and the highest depression scores were seen in caregivers. Contrarily, the highest personal success scores were seen in specialist doctors and security guards. Working in the ICU was associated with increased depression, fear of COVID-19, and emotional exhaustion, whereas working in the outpatient clinic was associated with increased personal success scores. All these findings indicate that closer and frequent contact with patients with COVID-19 causes increased negative psychological outcomes in healthcare professionals. In pandemic hospitals, resident doctors and caregivers and healthcare professionals in ICU worked in close contact with longer durations. Moreover, the healthcare professionals in the ICU had to experience their colleagues' serious illness course and death due to COVID-19. While all these are already difficult and troublesome, when the unknowns about the COVID-19 pandemic are considered, it may lead to an increased psychological burden on these healthcare professionals, especially those working in the ICU.

Frontline healthcare professionals could be more accustomed to potentially distressing experiences than non-frontline professionals, thus showing a lower negative response to challenging situations (12,14). However, studies have shown that nurses and those who work in the frontline with close contact with patients and those who work for long hours have more frequent negative psychological outcomes among the healthcare professionals during the COVID-19 pandemic (4). Moreover, these studies were conducted in the acute phase of the pandemic and included only specific occupational groups. Contrarily, this current study included all hospital staff working in COVID-19 pandemic hospitals serving patients with COVID-19 only. All participants were the frontline healthcare professionals since they worked in a pandemic hospital. Therefore, we think that our study predicts the relationship of psychosocial adjustment with the hospital unit and occupational groups in frontline healthcare professionals better than the previous studies.

The World Health Organization and the scientific world emphasize the importance of prevention methods for

the disease spread in the general population and health care professionals from the beginning of the pandemic. Special equipment and working hours arrangements were recommended for healthcare professionals. However, particularly at the beginning of the pandemic, as in many other countries, adequate equipment was not provided in many health institutions in Turkey, and medical doctors in different specialties had to work in COVID-19 outpatient and inpatients clinics with long working hours. Thus, we thought that frequent and unexpected changes in workplaces might lead to anxiety, hopelessness, and burnout in healthcare professionals.

This study examined the COVID-19 knowledge and attitudes of healthcare professionals. A majority reported that they were following new literature on COVID-19 and believed that the pandemic would end. In addition, a majority reported the insufficient provision of protection for COVID-19 infection from their institution. An inverse relation was demonstrated between the COVID-19 attitude and psychological adjustment in the healthcare professionals. In healthcare professionals, insufficient protection from COVID-19 means increased risk not only for getting sick but also for carrying the disease to their families. These thoughts lead to further social isolation within the family. All these factors were thought to increase the psychological burden on healthcare professionals and result in negative psychological outcomes. Similar studies emphasize that healthcare professionals are concerned about the protection or safety of themselves and their families from the disease, which is also another important stress factor (29). Trumella et al. (14) also state that a negative COVID-19 attitude can affect healthcare professionals mentally and even negatively affect their work performance.

Social support is one of the most important resources to cope with the psychological burden following the pandemic (29). Social support given to medical staff reduced anxiety and stress levels and increased their self-efficacy. Keeping stable working teams, improving communication and recognition, and providing clear guidelines and social support are examples of how the working environment could be improved during the pandemic (4,30).

Our study findings showed a negative relationship between social support and anxiety, depression, emotional exhaustion, depersonalization, and fear of COVID-19. COVID-19 attitude was more negative in those with low social support. Social support differed in occupational groups. Caregivers, resident doctors, and nurses had lower social support than others. The highest social support was seen in specialist doctors and outpatient clinic staff.

Our study results pointed out that the psychological adjustment and COVID-19 attitude of healthcare professionals working at the frontline during the COVID-19 pandemic were negatively affected, especially in those with lower social support. In addition, higher social support was associated with personal achievement. These findings were consistent with the literature. Our most striking finding related to social support was that healthcare professionals who work closely and have frequent contact with patients with COVID-19 had lower social support. These healthcare professionals themselves may be avoiding social contact because of their higher disease-carrying risk. Moreover, they may be isolated by their social environment and even by their family member. Especially in the first months of the pandemic, when the news in media warned many people in the society to stay away from healthcare professionals and healthcare professionals are labeled as contagious.

Study Limitations

The major limitation of this study was its cross sectionality. Another limitation is the sample. The subgroups of the sample had different educational levels with probable different socio-cultural and economic levels. In addition, this study was carried out on only one side of Istanbul and did not include the health care professionals from rural areas of the same city or country. However, the risk of transmission and lack of resources remains a common problem in healthcare facilities all around the country and future research needs to examine the experiences of healthcare workers within the rural hospitals as well.

CONCLUSION

This study evaluated the psychosocial adaptation of the healthcare professionals in a multidimensional approach, considering many areas, including depression, general anxiety, phobic anxiety specifically towards the COVID-19 disease, and hopelessness. Consistent with the literature, results showed that healthcare professionals were negatively affected by the COVID-19 pandemic process in terms of psychosocial adjustment. In addition, study results indicate that gender, occupation, and hospital unit are important factors for psychosocial adjustment during the pandemic. Moreover, psychosocial adjustment showed to be related to social support and the COVID-19 attitude of the healthcare professionals. Today, the COVID-19 pandemic continues. In the long run, the life quality and functionality of healthcare professionals should be considered. Our study results indicated that healthcare professionals who have high contact with patients with COVID-19 have high anxiety for themselves and their families. Therefore, planning for

psychosocial support programs and providing psychiatrist or psychologist assistance at regular intervals is thought to be important for healthcare workers. In addition, social support can be provided to health workers through institutions, associations, and professional organizations. Considering that the pandemic process will continue and new or different pandemic processes may emerge, providing adequate protective equipment against the specific infectious disease, providing adequate rest periods, and determining a regular job and place for health workers in the frontlines during the epidemics will have a more functional result in their psychosocial adjustment and professional lives. This study revealed the healthcare professionals that have increased risk for psychosocial adjustment problems, study results are valuable for both healthcare professionals and hospital managers, as well as the governments.

Acknowledgments

The authors would like to thank all the participants who kindly agreed to participate in the study.

ETHICS

Ethics Committee Approval: This study was conducted according to the provisions of the Declaration of Helsinki in 1995. Approval was obtained from the Ethics Committee of the same hospital with the University of Health Sciences Turkey, Bakirköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2020-157).

Informed Consent: Written and verbal consent of each participant was obtained.

Authorship Contributions

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

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. Porta M. A Dictionary of Epidemiology. 6th edit. Oxford university press; New York: 2014.
2. Republic of Turkey Ministry of Health, 2021. Covid-19 information page. https://covid19.saglik.gov.tr/EN-69532/general-coronavirus-table.html. Accessed on 8.5.2021
3. Banerjee D, Rai M. Social isolation in Covid-19: The impact of loneliness. Int J Soc Psychiatry 2020;66:525-7.
4. Zerbini G, Ebigbo A, Reicherts P, Kunz M, Messman H. Psychosocial burden of healthcare professionals in times of COVID-19 - a survey conducted at the University Hospital Augsburg. Ger Med Sci 2020;18:Doc05.
5. Hacimusalar Y, Kahve AC, Yasar AB, Aydin MS. Anxiety and hopelessness levels in COVID-19 pandemic: A comparative study of healthcare professionals and other community sample in Turkey. J Psychiatr Res 2020;129:181-8.
6. Gica S, Kavakli M, Durduran Y, Ak M. The Effect of COVID-19 Pandemic on Psychosomatic Complaints and Investigation of The Mediating Role of Intolerance to Uncertainty, Biological Rhythm Changes and Perceived COVID-19 Threat in this Relationship: A Web-Based Community Survey. Psychiatry and Clinical Psychopharmacology 2020;30:89-96.
7. Cullen W, Gulati G, Kelly BD. Mental health in the COVID-19 pandemic. QJM 2020;113:311-2.
8. Shah K, Chaudhari G, Kamrai D, Lail A, Patel RS. How Essential Is to Focus on Physician's Health and Burnout in Coronavirus (COVID-19) Pandemic? Cureus 2020;12:e7538.
9. Kisely S, Warren N, McMahon L, Dalais C, Henry I, Siskind D. Occurrence, prevention, and management of the psychological effects of emerging virus outbreaks on healthcare workers: rapid review and meta-analysis. BMJ 2020;369:m1642.
10. Spoorthy MS, Pratapa SK, Mahant S. Mental health problems faced by healthcare workers due to the COVID-19 pandemic-A review. Asian J Psychiatr 2020;51:102119.
11. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open 2020;3:e203976.
12. Kang L, Ma S, Chen M, Yang J, Wang Y, Li R, et al . Impact on mental health and perceptions of psychological care among medical and nursing staff in Wuhan during the 2019 novel coronavirus disease outbreak: A cross-sectional study. Brain Behav Immun 2020;87:11-7.
13. García-Reyna B, Castillo-García GD, Barbosa-Camacho FJ, Cervantes-Cardona GA, Cervantes-Pérez E, Torres-Mendoza BM, et al. Fear of COVID-19 Scale for Hospital Staff in Regional Hospitals in Mexico: a Brief Report. Int J Ment Health Addict 2020:1-12.
14. Trumello C, Bramanti SM, Ballarotto G, Candelori C, Cerniglia L, Cimino S, et al. Psychological Adjustment of Healthcare Workers in Italy during the COVID-19 Pandemic: Differences in Stress, Anxiety, Depression, Burnout, Secondary Trauma, and Compassion Satisfaction between Frontline and Non-Frontline Professionals. Int J Environ Res Public Health 2020;17:8358.
15. Hu D, Kong Y, Li W, Han Q, Zhang X, Zhu LX, et al. Frontline nurses' burnout, anxiety, depression, and fear statuses and their associated factors during the COVID-19 outbreak in Wuhan, China: A large-scale cross-sectional study. EClinicalMedicine 2020;24:100424.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
17. Aydemir Ö, Güvenir T, Küey L, Kültür S. Reliability and Validity of the Turkish version of Hospital Anxiety and Depression Scale. Turkish journal of psychiatry 1997;8:280-7.
18. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol 1974;42:861-5.
19. Durak A, Palabıyıkoğlu R. Beck Hopelessness Scale: reliability and validity. J Kriz 1994; 2:311-9.
20. Maslach V, Jackson SE. Maslach Burnout Inventory Manual. Palo Alto, CA: Consulting Psychologist Press; 1986.
21. Ergin C. Burnout in doctors and nurses, and adaptation of the maslach burnout scale. In Bayraktar R, Dağ I (eds): VII. National Psychology Congress Scientific Studies Turkish Psychological Association publishing; 1992. p. 143-54.

22. Ahorsu DK, Lin CY, Imani V, Saffari M, Griffiths MD, Pakpour AH. The Fear of COVID-19 Scale: Development and Initial Validation. Int J Ment Health Addict 2020:1-9.
23. Ladikli N, Bahadır E, Yumuşak FN, Akkuzu H, Karaman G, Türkkan Z. The reliability and validity of Turkish version of coronavirus anxiety scale. International journal of social sciences 2020;3:71-80.
24. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess 1988;52:30-41.
25. Eker D, Arkar H, Yaldız H. Factorial Structure, Validity, and Reliability of the Multidimensional Scale of Perceived Social Support. Turkish journal of psychiatry 2001;12:17-25.
26. Yas Coskun S, Bildik F, Aslaner MA, Aslan S, Keles A, Kilicaslan I, et al. The Effect of the COVID-19 Pandemic on the Psychological Status of Hospital Workers. Psychiatry and Clinical Psychopharmacology 2020;30:264-72.
27. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. Brain Behav Immun 2020;88:901-7.
28. Newman MG, Shin KE, Zuellig AR. Developmental risk factors in generalized anxiety disorder and panic disorder. J Affect Disord 2016;206:94-102.
29. Xiao H, Zhang Y, Kong D, Li S, Yang N. The Effects of Social Support on Sleep Quality of Medical Staff Treating Patients with Coronavirus Disease 2019 (COVID-19) in January and February 2020 in China. Med Sci Monit 2020;26:e923549.
30. Petzold MB, Plag J, Ströhle A. Umgang mit psychischer Belastung bei Gesundheitsfachkräften im Rahmen der COVID-19-Pandemie [Dealing with psychological distress by healthcare professionals during the COVID-19 pandemia]. Nervenarzt 2020;91:417-21.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:386-391
DOI: 10.4274/BMJ.galenos.2021.75437

Research

Association of TG/HDL Ratio with Cardiovascular Mortality in Patients Who are on Hemodialysis

Hemodiyalize Giren Son Dönem Böbrek Yetersizliği Hastalarında TG/HDL Oranı ile Kardiyovasküler Ölüm Arasındaki İlişki

Umut Karabulut[1], Gülay Yılmaz[2]

[1]Acıbadem International Hospital, Clinic of Cardiology, Istanbul, Turkey
[2]Acıbadem International Hospital, Clinic of Nephrology and Transplantation, Istanbul, Turkey

ABSTRACT

Objective: There is a relation between triglyceride/high-density lipoprotein (TG/HDL) ratio, and cardiovascular and all-cause mortality. No study has been conducted on this relationship in cases with end-stage renal disease who are on hemodialysis in Turkey. Therefore, we aimed to see the relation between TG/HDL ratio and cardiovascular mortality in hemodialysis patients.

Methods: This study included 344 cases who were aged ≥18 years and on hemodialysis. These cases were divided into two groups as cardiovascular death (n=31) and survivors (n=313). Primary endpoint of this study was cardiovascular mortality.

Results: Among 344 patients, 74.1% were males, and the mean age was 43.7±12.6 years. Dialysis duration was 1.1 (3.1) years, and the total follow-up duration was 5.9 (2.9) years. TG/HDL ratio was similar in both groups (p>0.05). Age [human resource (HR): 1.02, 95% confidence interval (CI): (1,055-1.09), p=0.02], HbA1c [HR: 1,292, 95% CI: (1,080-1,546), p=0.05], and TG/HDL ratio [HR: 1,078, 95% CI: (1,009-1.51), p=0.026] were independent predictors of cardiovascular mortality. Kaplan-Meier curves revealed that cardiovascular mortality was higher in the group using fenofibrate [p (log-rank) =0.01].

Conclusion: TG/HDL ratio is an inexpensive, simply applicable tool that may predict cardiovascular mortality in hemodialysis patients. Therefore, it may significantly benefit in optimizing cardiovascular risk management and treatment goals in these patients.

Keywords: TG/HDL ratio, end-stage renal disease, hemodialysis, cardiovascular mortality

ÖZ

Amaç: Trigliserit/yüksek yoğunluklu lipoprotein (TG/HDL) oranı ile kardiyovasküler ve tüm nedenlere bağlı ölüm arasında bir ilişki olduğu bilinmektedir. Ülkemizde hemodiyalize giren son dönem böbrek yetersizliği hastalarında bu ilişkiyi inceleyen çalışma yapılmamıştır. Bu nedenle çalışmamızda hemodiyaliz hastalarında TG/HDL oranı ile kardiyovasküler ölüm arasında bulunan ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya 18 yaş ve üzerinde, hemodiyalize giren son dönem böbrek yetersizliği tanısı almış 344 hasta dahil edildi. Hastalar kardiyovasküler sebeplerle ölen (n=31) ve sağ kalan (n=313) hasta olarak ikiye bölündü. Çalışmanın birincil sonlanım noktası kardiyovasküler ölüm idi.

Bulgular: Çalışmaya alınan 343 hastanın %74,1'i erkek olup, yaş ortalaması 43,7±12,6 idi Ortalama diyaliz süresi 1,1 (3,1) yıl, toplam takip süresi ise 5,9 (2,9) yıldı. TG/HDL oranı her iki grupta da benzerdi (p>0,05). Yaş [human kaynak (HR): 1,02 %95 güven aralığı (CI): (1.055-1,09), p=0,02], HbA1c [HR: 1.292 %95 CI: (1.080-1.546), p=0,05] ve TG/HDL oranı [HR: 1.078 %95 CI: (1.009-1,51), p=0,026], kardiyovasküler ölümün bağımsız öngörücüleri olarak bulundu. Kaplan-Meier eğrileri, fenofibrat kullanan grupta kardiyovasküler mortalitenin anlamlı olarak daha yüksek olduğunu ortaya koydu [p (log-rank) =0,01].

Sonuç: TG/HDL oranı hemodiyaliz hastalarında kardiyovasküler mortaliteyi öngörebilen ucuz, kolay uygulanabilir bir yöntemdir. Bu nedenle, bu hastaların kardiyovasküler risk yönetiminde ve tedavi hedeflerini optimize etmede önemli bir fayda sağlayacaktır.

Anahtar Kelimeler: TG/HDL oranı, son dönem böbrek yetersizliği, hemodiyaliz, kardiyovasküler ölüm

Address for Correspondence: Umut Karabulut, Acıbadem International Hospital, Clinic of Cardiology, Istanbul, Turkey
Phone: +90 532 548 58 05 E-mail: drgulaytastan@hotmail.com ORCID ID: orcid.org/0000-0002-3947-9173

Cite as: Karabulut U, Yılmaz G. Association of TG/HDL Ratio with Cardiovascular Mortality in Patients who are on Hemodialysis. Med J Bakirkoy 2021;17:386-391

Received: 13.09.2021
Accepted: 01.10.2021

INTRODUCTION

Although hemodialysis-related complications gradually decrease in cases with end-stage renal disease (ESRD), mortality rates are still greater than that of the normal population. As expected, a significant proportion of this is cardiovascular mortality (1). As traditional risk factors are inadequate to define cardiovascular outcomes in patients with ESRD, practical, easily applicable, new risk markers are frequently sought in this area (2-4).

Lipid disorder is common in ESRD cases, and triglyceride (TG) level is high and high-density lipoprotein (HDL) level is low (5). Pathophysiologically, high TG levels and low HDL levels interact during lipid metabolism, and each alone is a risk factor for atherosclerosis. TG/HDL ratio is a practical, validated tool, which better demonstrates this complex interaction in ESRD patients with dyslipidemia (6). It is known that a high TG/HDL ratio is associated with metabolic syndrome, hypertension (HTN), diabetes, and cardiovascular events (7-10). Furthermore, it is proven that there is a significant relationship between TG/HDL ratio and cardiovascular and all-cause mortality (11,12).

Many studies have revealed the relationship between TG/HDL ratio and cardiovascular events in ESRD patients, but these results have been controversial (13-15). Moreover, no study has been conducted only in cases with ESRD who are on hemodialysis in our country. Therefore, we aimed to see the relation between TG/HDL ratio and cardiovascular mortality in the hemodialysis patients.

METHODS

This study included patients aged ≥18 years who were undergoing hemodialysis between 2015 and 2020. All the patients were divided into two groups: group 1, cardiovascular death (n=31) and group 2, survivors (n=313).

Patients who were <18 years of age, with peritoneal dialysis (n=23), or who died from non-cardiac causes (n=9) were removed from the study. Approval for the study was granted by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Regional Ethics Committee (no: 2021-14-11, date: 12/07/2021). All the participants' rights were protected, and written informed consent was taken from the patients before the procedures.

Demographic data and laboratory findings of cases were collected from Nephrology Clinic Database. Etiology of ESRD, duration of hemodialysis, and cardiac mortality were recorded. Hemogram, routine biomarkers, and total cholesterol (TC), HDL-C, LDL-C, TG, and non-HDL-C values were recorded. Traditional cardiovascular risk factors, history of cardiovascular disease, and coronary revascularization were recorded along with the use of lipid-lowering drugs.

Fasting blood tests included TC, LDL-C, HDL-C, non-HDL-C, and TG. TG was determined using the enzymatic color method (Biotrol), and TC with the photometric method (Siemens, Dimension EXL 200, Germany). The TG/HDL ratio was calculated. Primary endpoint of this study was cardiovascular mortality.

Statistical Analysis

Data were analyzed statistically using SPSS (Version 20 software). We confirmed continuous variables to be normally distributed according to the Kolmogorov-Smirnov test. Demographic, clinical, and laboratory values of the two groups were compared by using a t-test or the Mann-Whitney U test for continuous variables according to the distribution pattern of the data. Chi-square test or Fischer's Exact test were used to compare the categorical data. Kaplan-Meier survival analysis was conducted for cardiovascular mortality, and log-rank test was used to compare the two curves. Cox proportional hazard regression analysis was applied with cardiovascular mortality assigned as a dependent variable. Covariates with p-value <0.15 or those which were clinically significant were entered into the multivariate model. For all analyses, a two-sided p-value <0.05 was considered as statistically significant.

RESULTS

An evaluation was made of 344 patients, comprising 74.1% males and 25.9% females. Mean age was 43.7±12.6 years. The group with mortality was older than the survivors' group (p>0.001). A history of HTN, diabetes mellitus (DM), or coronary artery disease (CAD) was greater in the non-survival group than in the survivors' group (p=0.034, p<0.001, p<0.001, respectively). Mean hemodialysis duration was similar in both groups (p=0.615) (Table 1).

Fenofibrate usage was greater in the non-survival group than in the survivors' group (p=0.038)

Glucose and HbA1c levels were greater in the non-survival group (p<0.001, p=0.002, respectively). Other laboratory parameters and TG/HDL ratio were similar in two groups (p>0.05 for all). Baseline characteristics and laboratory parameters of the cases are shown in Table 1.

Dialysis duration was 1.1 (3.1) years, and the total follow-up duration was 5.9 (2.9) years. Survivors' group was followed-up significantly longer than the non-survival group (p<0.01) (Table 1).

Table 1. Baseline characteristics and laboratory findings of all the study participants

Variables	Total (n=343)	Non-mortal (n=312)	Mortal (n=31)	p
Gender (male), n %	254 (74.1)	229 (73.4)	25 (80.6)	0.380
Age (years)	43.7±12.6	42.9±12.6	52.0±10.4	**<0.001**
BMI (kg/m^2)	25.2±4.8	25.1±4.9	26.1±3.5	0.271
HTN, n (%)	128 (37.3)	111 (35.6)	17 (54.8)	**0.034**
DM, n (%)	81 (23.6)	64 (20.5)	17 (54.8)	**<0.001**
Smoking, n (%)	42 (12.2)	36 (11.5)	6 (19.4)	0.245
CAD history, n (%)	56 (16.3)	43 (13.8)	13 (41.9)	**<0.001**
Dialysis duration (years)	1.1 (3.1)	1.1 (3.4)	1.1 (2.8)	0.615
Follow-up (years)	5.9 (2.9)	6.1 (2.7)	2.6 (3.6)	**<0.001**
Medications, n (%)				
Fenofibrate	22 (6.4)	17 (5.4)	5 (16.1)	0.038
Statin	40 (11.7)	35 (11.2)	5 (16.1)	0.384
Laboratory findings				
BUN (mg/dL)	54 (26)	54.5 (26.8)	47 (26)	0.085
Creatinine, (mg/dL)	8.3±2.9	8.4±2.9	7.3±2.8	0.053
Sodium, (mg/dL)	137.6±3.3	137.6±3.4	138.2±2.5	0.348
Potassium, (mg/dL)	5.1±0.8	5.2±0.8	4.7±0.7	0.130
Calcium, (mg/dL)	9.1±0.9	9.1±0.9	8.9±0.8	0.288
Uric acid, (mg/dL)	5.6±1.6	5.7±1.6	5.3±1.6	0.281
Albumin, (mg/dL)	4.1±0.6	4.1±0.6	4.0±0.8	0.504
Glucose, (mg/dL)	91 (24)	91 (19)	108 (57)	**<0.001**
HbA1C	5.7±1.4	5.6±1.3	6.8±1.9	**0.002**
TC, (mg/dL)	188.9±45.4	187.9±42.3	199.5±68.9	0.173
LDL-C, (mg/dL)	116.9±36.2	116.8±35.6	118.3±42.6	0.827
HDL-C, (mg/dL)	50.9±16.7	51.1±16.9	48.6±15.1	0.425
Triglyceride, (mg/dL)	158 (111)	154.5 (111.8)	170 (92)	0.251
TG/HDL ratio	3.2 (3.3)	3.9 (2.7)	3.5 (4.4)	0.237
WBC (x10^3/uL)	7.5±2.3	7.5±2.3	7.9±2.7	0.219
Hb (g/dL)	11.5±1.9	11.4±1.9	11.5±1.6	0.788
Platelet (x10^3/uL)	219.3±71.3	218.8±71	223.9±75.5	0.706

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, WBC: White blood cell, Hb: Hemoglobin

During the follow-up, deaths due to cardiovascular causes were recorded in a total of 31 patients, of which 19 were due to myocardial infarction, 5 to sudden cardiac death, and 7 to stroke.

Cox regression analysis was performed to determine the predictors of cardiac mortality. Variables found to be significant in univariate analysis or with clinical relevance were included in the multivariate analysis. Age, HTN, DM, CAD history, fenofibrate usage, creatinine, HbA1c, TG, and TG/HDL ratio were found to be significant in univariate analysis. (p<0.001, p=0.026, p=0.001, p=0.015, p=0.035, p<0.001, p=0.02, p=0.006, respectively) (Table 2). Only age [human resource (HR): 1.02, 95% confidence interval (CI): (1,055-1.09), p=0.02], HbA1c [HR: 1,292, 95% CI: (1,080-1,546), p=0.05], and TG/HDL ratio [HR: 1,078, 95% CI: (1,009-1.51), p=0.026] were independent predictors of cardiovascular mortality (Table 2).

Table 2. Univariate and multivariate Cox regression analyses for cardiac mortality

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	HR (95% CI)	p
Sex (male)	1.316 (0.539-3.209)	0.546	-	-
Age (years)	1.061 (1.028-1.095)	**<0.001**	1.020 (1.055-1.090)	**0.002**
BMI	1.040 (0.969-1.116)	0.276	-	-
HTN	2.240 (1.103-4.550)	**0.026**	-	-
DM	3.400 (1.667-6.934)	**0.001**	-	-
Smoking	2.011 (0.825-4.905)	0.124	-	-
CAD history	3.726 (1.822-7.623)	**<0.001**	-	-
Dialysis duration	0.982 (0.888-1.086)	0.723	-	-
Fenofibrate	3.284 (1.256-8.588)	**0.015**	-	-
Statin	1.411 (0.541-3.678)	0.481	-	-
BUN (mg/dL)	1.005 (0.998-1.012)	0.168	-	-
Creatinine (mg/dL)	0.856 (0.741-0.989)	**0.035**	-	-
Sodium (mg/dL)	1.01 (0.956-1.156)	0.306	-	-
Potassium (mg/dL)	0.666 (0.423-1.048)	0.079	-	-
Calcium (mg/dL)	0.738 (0.499--1.092)	0.129	-	-
Uric acid (mg/dL)	0.834 (0.661-1.053)	0.128	-	-
Albumin (mg/dL)	0.637 (0.358-1.132)	0.124	-	-
Glucose (mg/dL)	1.004 (0.999-1.008)	0.101	-	-
HbA1C	1.395 (1.184-1.643)	**<0.001**	1.292 (1.080-1.546)	**0.005**
TC, (mg/dL)	1.005 (0.998-1.012)	0.168	-	-
LDL-C, (mg/dL)	1.001 (0.991-1.011)	0.832	-	-
HDL-C, (mg/dL)	0.988 (0.965-1.011)	0.295	-	-
Triglyceride, (mg/dL)	1.002 (1.000-1.003)	**0.020**	-	-
TG/HDL ratio	1.087 (1.024-1.155)	**0.006**	1.078 (1.009-1.151)	**0.026**
WBC ($x10^3$/uL)	1.000 (1.000-1.000)	0.171	-	-
Hb (g/dL)	1.024 (0.841-1.246)	0.814	-	-
Platelet ($x10^3$/uL)	1.000 (1.000-1.000)	0.646	-	-

BMI: Body mass index, HTN: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, WBC: White blood cell, Hb: Hemoglobin, OR: Odds ratio, CI: Confidence interval

Kaplan-Meier curves showed that cardiovascular mortality was greater in the group using fenofibrate [p (log-rank) =0.01] (Figure 1).

DISCUSSION

The findings of this study revealed that TG/HDL ratio is an independent predictor for cardiovascular mortality in hemodialysis cases. As expected, the non-survival group was older, and the rates of HTN, DM, and CAD were higher than in the surviving cases. A remarkable finding in the current study in terms of laboratory findings was that the TG and TG/HDL ratio in the cardiac death group was not different from that of the survivors' group. This was thought to be due to the significantly higher usage of fenofibrate in the non-survival group.

One of the main risk factors for cardiovascular diseases in hemodialysis patients is dyslipidemia, which also contributes to decreased physical capacity and weight

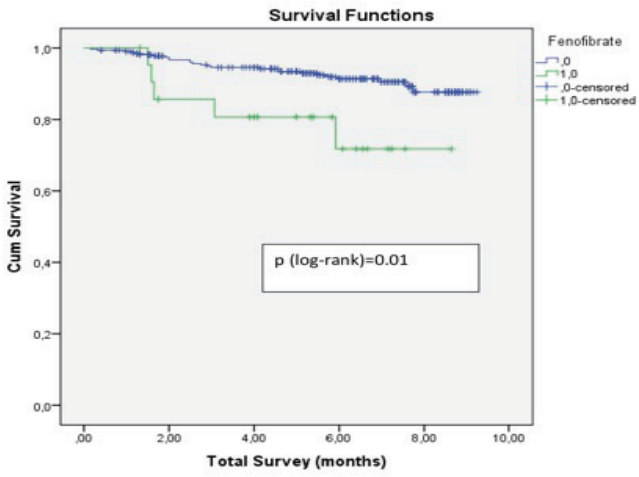

Figure 1. Kaplan-Meier curves revealed that cardiovascular mortality was significantly higher in the group using fenofibrate [p (log-rank) =0.01]

loss (16,17). Dyslipidemia is related to many factors such as diabetes, HTN, renal replacement treatment, and drugs used by the hemodialysis patients (18). It is thought that the TG/HDL ratio predicts cardiovascular outcomes better than the measurement of lipid levels alone, since an increase in TG and a decrease in HDL are prominent in these patients (19). Chen et al. (20) showed that high TG/HDL ratio increases the cardiac mortality in patients undergoing both hemodialysis (most of the patients) and peritoneal dialysis, and these results are consistent with those of the current study. Chang et al. (21) published a large-scale study that included only ESRD patients undergoing hemodialysis. Unlike the current study, a significant correlation was seen between a high TG/HDL ratio and low cardiac mortality (21). These conflicting results are attributed to the complex nature of lipid metabolism in dialysis, differences in patient numbers, ethnicity, inclusion criteria, etc. Nevertheless, the mechanism has not been elucidated. In addition to the huge patient population in the study by Chang et al. (21), the results may be considered more valuable due to its prospective design. The results were consistent with those of the current study. The new aspect of this study was the larger number of patients with the advanced renal failure who underwent dialysis. Another remarkable finding in this study was that the survival of the patients using fenofibrate was significantly lower than that in the non-users. This result seems to be the opposite of expectations. The reason for this unexpected result was thought to be that the target TG goals could not be reached in ESRD patients using fenofibrate (due to low dose or irregular use). Many studies have revealed that LDL-C is not a very strong predictor of mortality in hemodialysis patients. There is no significant reduction in cardiovascular mortality with statin (22-24). Therefore, in these cases, TG reduction with aggressive fenofibrate treatment is much more critical.

Study Limitations

This study was retrospective, single-center, and cross-sectional in design. The frequency of dialysis and the medications taken (except lipid drugs) might have affected the cardiac outcomes. The lack of these data could be considered as another limitation.

CONCLUSION

In conclusion, TG/HDL ratio is an inexpensive, easily applicable tool that may predict cardiac mortality in hemodialysis patients. It will provide significant benefits in optimizing cardiovascular risk management, and treatment goals in these patients. Nevertheless, there is a need for conducting multicenter, prospective, large-scale studies in the future for these results.

ETHICS

Ethics Committee Approval: Approval for the study was granted by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Regional Ethics Committee (no: 2021-14-11, date: 12/07/2021).

Informed Consent: Written informed consent was taken from the patients before the procedures.

Authorship Contributions

Surgical and Medical Practices: G.Y., Concept: U.K., Design: G.Y., Data Collection or Processing: U.K., Analysis or Interpretation: G.Y., Literature Search: U.K., Writing: U.K., G.Y.

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. US Renal Data System: USRDS 2015 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2015.
2. Neuen BL, Leather N, Greenwood AM, Gunnarsson R, Cho Y, Mantha ML. Neutrophil-lymphocyte ratio predicts cardiovascular and all-cause mortality in hemodialysis patients. Ren Fail 2016;38:70-6.
3. Chang YM, Huang YT, Chen IL, Yang CL, Leu SC, Su HL, et al. Heart rate variability as an independent predictor for 8-year mortality among chronic hemodialysis patients. Sci Rep 2020;10:881.
4. Fitzpatrick J, Sozio SM, Jaar BG, Estrella MM, Segev DL, Parekh RS, et al. Frailty, body composition and the risk of mortality in

incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study. Nephrol Dial Transplant 2019;34:346-54.

5. Ritz E, Wanner C. Lipid abnormalities and cardiovascular risk in renal disease. J Am Soc Nephrol 2008;19:1065-70.
6. Wan K, Zhao J, Huang H, Zhang Q, Chen X, Zeng Z, et al. The association between triglyceride/high-density lipoprotein cholesterol ratio and all-cause mortality in acute coronary syndrome after coronary revascularization. PLoS One 2015;10:e0123521.
7. Moriyama K. Associations Between the Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Metabolic Syndrome, Insulin Resistance, and Lifestyle Habits in Healthy Japanese. Metab Syndr Relat Disord 2020;18:260-6.
8. Young KA, Maturu A, Lorenzo C, Langefeld CD, Wagenknecht LE, Chen YI, et al. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio as a predictor of insulin resistance, β-cell function, and diabetes in Hispanics and African Americans. J Diabetes Complications 2019;33:118-22.
9. Vega GL, Barlow CE, Grundy SM, Leonard D, DeFina LF. Triglyceride-to-high-density-lipoprotein-cholesterol ratio is an index of heart disease mortality and of incidence of type 2 diabetes mellitus in men. J Investig Med 2014;62:345-9.
10. Yeom H, Kim HC, Lee JM, Jeon Y, Suh I. Triglyceride to high density lipoprotein cholesterol ratio among adolescents is associated with adult hypertension: the Kangwha study. Lipids Health Dis 2018;17:212.
11. Bittner V, Johnson BD, Zineh I, Rogers WJ, Vido D, Marroquin OC, et al. The triglyceride/high-density lipoprotein cholesterol ratio predicts all-cause mortality in women with suspected myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE). Am Heart J 2009;157:548-55.
12. Caselli C, Rocchiccioli S, Smit JM, Ragusa R, Rosendael R, Buechel, et al., EVINCI, and SMARTool studies, Elevated TG/HDL-C ratio, is an independent predictor of outcome, and it is associated with CAD progression in patients with stable coronary artery disease, European Heart Journal Issue 2020;41:2.
13. Wen J, Chen Y, Huang Y, Lu Y, Liu X, Zhou H, et al. Association of the TG/HDL-C and Non-HDL-C/HDL-C Ratios with Chronic Kidney Disease in an Adult Chinese Population. Kidney Blood Press Res 2017;42:1141-54.
14. Kim Y, Lee S, Lee Y, Kang MW, Park S, Park S, et al. Predictive value of triglyceride/high-density lipoprotein cholesterol for major clinical outcomes in advanced chronic kidney disease: a nationwide population-based study. Clin Kidney J 2020;14:1961-8.
15. Sonmez A, Yilmaz MI, Saglam M, Unal HU, Gok M, Cetinkaya H, et al. The role of plasma triglyceride/high-density lipoprotein cholesterol ratio to predict cardiovascular outcomes in chronic kidney disease. Lipids Health Dis 2015;14:29.
16. Vaziri ND, Moradi H. Mechanisms of dyslipidemia of chronic renal failure. Hemodial Int 2006;10:1-7.
17. Obi Y, Qader H, Kovesdy CP, Kalantar-Zadeh K. Latest consensus and update on protein-energy wasting in chronic kidney disease. Curr Opin Clin Nutr Metab Care 2015;18:254-62.
18. Moradi H, Vaziri ND. Molecular mechanisms of disorders of lipid metabolism in chronic kidney disease. Front Biosci (Landmark Ed) 2018;23:146-61.
19. Sultani R, Tong DC, Peverelle M, Lee YS, Baradi A, Wilson AM. Elevated Triglycerides to High-Density Lipoprotein Cholesterol (TG/HDL-C) Ratio Predicts Long-Term Mortality in High-Risk Patients. Heart Lung Circ 2020;29:414-21.
20. Chen HY, Tsai WC, Chiu YL, Hsu SP, Pai MF, Yang JY, et al. Triglyceride to high-density lipoprotein cholesterol ratio predicts cardiovascular outcomes in prevalent dialysis patients. Medicine (Baltimore) 2015;94:e619.
21. Chang TI, Streja E, Soohoo M, Kim TW, Rhee CM, Kovesdy CP, et al. Association of Serum Triglyceride to HDL Cholesterol Ratio with All-Cause and Cardiovascular Mortality in Incident Hemodialysis Patients. Clin J Am Soc Nephrol 2017;12:591-602.
22. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, et al. Association between LDL-C and risk of myocardial infarction in CKD. J Am Soc Nephrol 2013;24:979-86.
23. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48.
24. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:392-399
DOI: 10.4274/BMJ.galenos.2021.2021.10-10

Research

The Effect of Body Mass Index on the Mortality of Patients Followed up in the Intensive Care Unit with COVID-19 Diagnosis

Yoğun Bakım Ünitesinde COVID-19 Tanısı ile Takip Edilen Hastalarda Beden Kitle İndeksinin Mortaliteye Etkisi

Duygu Akyol[1], Rabia Yılmaz[2], Nalan Saygı Emir[3]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Critical Care Medicine, Istanbul, Turkey
[3]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey

ABSTRACT

Objective: The Coronavirus disease-2019 (COVID-19) pandemic continues its effect worldwide. Studies that examine the relationship between the body mass index (BMI) and COVID-19 have reported inconsistent results. Thus, this study aimed to investigate the effect of BMI on severe COVID-19 and mortality to resolve this uncertainty between BMI and COVID-19.

Methods: This study was designed as a retrospective cohort study and was conducted by analyzing data from 219 patients with a diagnosis of COVID-19 who were followed up at University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Training and Research Hospital between March 15, 2021, and August 15, 2021.

Results: Patients were divided into two groups as obese (n=53; 24.2%) and nonobese (n=166; 75.8%) patients. Males were more prevalent in the obese group, whereas females were more prevalent in the nonobese group. The incidence of diabetes mellitus and chronic obstructive pulmonary disease (COPD) was found higher in patients with obesity than those without obesity (p<0.005). Disease severity scores calculated after the intensive care unit (ICU) admission were similar in both groups. The incidence of arterial and central venous catheters was found to be higher in patients with obesity (p<0.05). The incidence of acute kidney injury was found to be more prevalent in patients with obesity (p<0.05). The Ppeak was higher in patients with obesity in the mechanical ventilator parameters; however, their tidal volume was found to be lower (p<0.05). Mechanical ventilation time and ICU stay were observed to be higher in patients with obesity (p<0.05). Mortality rates were similar in patient with obesity (n=83; 50%) and without (n=27; 50.9%).

Conclusion: Our research results revealed similar ICU scores and laboratory values; however, patients with obesity had longer ICU stay and mechanical ventilation periods. Further, no relationship was found between BMI and mortality.

Keywords: COVID-19, Coronavirus, obesity, body mass index, critical care, mortality

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pandemisi tüm dünyayı etkilemeye devam etmektedir. Beden kitle indeksi (BKİ) ve COVID-19 ilişkisini araştıran çalışmalar, BKİ ve COVID-19 arasındaki ilişki hakkında tutarsız sonuçlar bildirmiştir. Bu araştırma BKİ ve COVID-19 arasındaki bu belirsizliği gidermek amacıyla BKİ'nin şiddetli COVID-19 ve mortalite üzerine etkisini belirlemek amacıyla planlandı.

Gereç ve Yöntem: Retrospektif kohort olarak planlanan bu araştırma 15 Mart 2021-15 Ağustos 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi'nde takip edilen COVID-19 tanılı 219 hastanın verileri analiz edilerek gerçekleştirildi.

Results: Hastalar obez (53; %24,2) ve non-obez (166; %75,8) hastalar olmak üzere iki gruba ayrıldı. Obez hastalarda erkek, non-obez hastalarda kadın cinsiyet daha sık görüldü. Obez hastalarda diabetes mellitus ve kronik obstrüktif akciğer hastalığı görülme sıklığının, non-obez hastalardan daha yüksek olduğu saptandı (p<0,005). Yoğun bakım ünitesi (YBÜ) kabulü sonrası hesaplanan hastalık şiddeti skorları her iki grupta benzer

Address for Correspondence: Duygu Akyol, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
Phone: +90 5447616034 E-mail: dr.duyguaygun@gmail.com ORCID ID: orcid.org/0000-0001-7956-9942

Cite as: Akyol D, Yılmaz R, Saygı Emir N. The Effect of Body Mass Index on the Mortality of Patients Followed up in the Intensive Care Unit with COVID-19 Diagnosis. Med J Bakirkoy 2021;17:392-399

Received: 20.10.2021
Accepted: 15.11.2021

bulundu. Arter kateteri ve santral venöz kateter uygulanma sıklığı obez hastalarda daha yüksek bulundu (p<0,05). Obez hastalarda akut böbrek hasarı gelişme sıklığının arttığı saptandı (p<0,05). Mekanik ventilatör parametrelerinde obez hastalarda Ppeak daha yüksek olmasına rağmen tidal volum daha düşük bulundu (p<0,05). Mekanik ventilasyon süresi ve YBÜ kalış süresi obez hastalarda daha yüksek bulundu (p<0,05). Mortalite oranları obez (83; %50) ve non-obez (27; %50,9) hastalarda benzerdi.

Sonuç: Araştırmamız sonucunda YBÜ skorları ve laboratuar değerleri benzer olmasına rağmen obez hastaların YBÜ yatış süresi ve mekanik ventilasyon süresinin daha uzun olduğu belirlendi. Ancak, BKİ ve mortalite arasında ilişki bulunamadı.

Anahtar Kelimeler: COVID-19, Koronavirüs, obezite, beden kitle indeksi, yoğun bakım, mortalite

INTRODUCTION

On March 11, 2020, the World Health Organization proclaimed the Coronavirus disease-2019 (COVID-19) as a pandemic, which piqued public interest in an infectious disease rife with unknowns (1). The COVID-19 pandemic has inspired global research attempts to identify those who are most likely to suffer severe illness and die (2). Diabetes mellitus (DM), lung disorders, cardiovascular disease, and renal disease are all linked to an elevated risk of negative outcomes in COVID-19 individuals according to preliminary studies (3-5). Additionally, some studies have linked increased body mass index (BMI) and obesity with more severe COVID-19 and increased mortality (6-9).

Obesity is considered an important public health problem. DM was shown to be associated with cardiovascular disease, respiratory tract diseases, some types of cancer, and increased morbidity and mortality due to any cause (10-12). However, epidemiological studies and meta-analyses investigating the relationship between BMI and COVID-19 have reported inconsistent results about. While some studies suggest that increased BMI and obesity worsen the disease outcome (9,13,14), others suggest no effect on disease outcomes (15,16). Obesity is uncertain to be a risk factor for COVID-19 because of the disparities in the current research results. The relationship between the BMI and COVID-19 severity and risk of mortality is unclear.

Thus, this research aimed to investigate the effect of BMI on the severe COVID-19 and mortality to resolve this uncertainty between BMI and COVID-19.

METHODS

Data-center

The presented retrospective study was performed after the approval of the local ethics committee (number: 2021/413). This study was designed as a retrospective cohort and was conducted in the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital with 27 intensive care unit (ICU) level-3 beds in Istanbul, Turkey. Written informed consent was obtained from the patients and their relatives.

This center admits an average of 1,760 patients in the medical-surgical ICU annually. This closed unit provides intensive care services on a 24/7 basis in which extracorporeal treatments are performed by intensive care specialists, with a nurse-patient ratio of 1:2.

After removing the clothes of all patients who are admitted to the ICU, their height and weight are measured by the staff and recorded in the clinical decision support system. During this measurement, treatments such as intravenous fluids and diuretics are administered to the patient before the ICU admission. After entering the weight and height data, the BMI is calculated and automatically saved by the system. Thus, the patient's BMI value is quickly and precisely recorded.

Data Collection

The data of patients who were followed up between March 15, 2021, and August 15, 2021, were obtained using the Structured Query Language queries from the EMRall-QlinI CUImd Soft Metavision Clinical Decision Support System used in the ICU and were retrospectively analyzed. During the research period, all patients diagnosed with COVID-19 and admitted to the ICU were treated according to the Ministry of Health's published and revised recommendations (17). Demographic characteristics of patients, BMI values, length of stay, developing AMI warnings, disease severity scores calculated in the ICU, mean potential hydrogen (pH), partial pressure of oxygen (PO_2), and partial pressure of carbon dioxide (PCO_2) obtained from the blood gas samples taken in the ICU, lactate values, treatments (vasoactive drugs and antibiotics) and interventions applied in the ICU, mechanical ventilation parameters, such as respiratory rate per minute, positive end-expiratory pressure, the fraction of inspired oxygen, work of breathing ventilator, Tidal volume and P peak data, mechanical ventilation time, and mortality data were analyzed.

Sample

We aimed to sample all patients admitted to the ICU with the diagnosis of COVID-19 at the time of the research. During the research period, 28,260 outpatients were admitted to our hospital with a pre-diagnosis of COVID-19. A total of

1,870 patients with a confirmed diagnosis of COVID-19 were hospitalized. The ICU received 275 patients who had been diagnosed with COVID-19. After applying the exclusion criteria, 219 patients followed up in the ICU were included in the study.

Sample Criteria

All patients with COVID-19 over the age of 18 years, who were followed in the ICU for more than 24 h, were planned to be included in the study.

Exclusion Criteria

Patients younger than 18 years (n=1),

Patients admitted to the service within the first 24 h in the ICU (n=2),

Patients who developed mortality in the first 24 h in the ICU (n=22),

Patients with missing data (n=31).

Primary Result

Examining the effect of BMI on mortality in patients with COVID-19 was determined as the primary aim of the study.

Secondary Results

Patients' comorbidities, admission diagnoses, scores computed after admission to ICU, laboratory results, interventions and therapies, mechanical ventilator data, acute kidney injury (AKI) progression and stages, and ICU mortality were compared according to BMI categories as secondary goals of the study.

Statistical Analysis

The data collected in the study were analyzed using the Statistical Package for the Social Sciences 22.00 program. Categorical variables were presented as frequency (n) and percentage (%), numerical variables as mean and standard deviation, or median and interquartile ranges. The independent sample t-test and Mann-Whitney U test were used to compare numerical data. The Chi-square test and Fisher Exact test were utilized for categorical variables. Receiver-operating characteristic (ROC) analysis was used to examine the effect of BMI on ICU mortality and to determine the cut-off value to predict mortality. The statistical significance level was accepted as a p-value of <0.05.

Findings

A total of 219 patients who are admitted to the ICU during the study period were divided into two groups as patients with obesity (n=53; 24.2%) and those without obesity (n=166; 75.8%). Demographic characteristics and comorbidities of patients are given in Table 1. Males were more prevalent in the obese group, whereas females were more prevalent in the nonobese group. Patients with obesity were younger than those without obesity (p<0.05). Comorbid disease frequency and Charlson comorbidity index score were similar between the groups. Hypertension was found to be the most common comorbidity in both groups. The other comorbid diseases examination found that the incidence of DM and COPD in patients with obesity was higher than those without obesity (p<0.005). The frequency of other comorbid diseases was similar among the groups.

Table 1. Demographic characteristics and comorbidities of patients

Parameters	Non-obese (n=166; 75.8%)	Obese (n=53; 24.2%)	p
BMI, median (IQR)	26.0 (23.9-27.8)	33.1 (31.1-38.6)	-
Age, year (mean ± SD)	64 (50-73)	55 (48-69)	0.040
<50	39 (23.5)	15 (28.3)	0.480
50-59	31 (18.7)	17 (32.1)	0.040
60-69	41 (24.7)	8 (15.1)	0.144
70-79	31 (18.7)	10 (18.9)	0.975
≥80	24 (14.5)	3 (5.7)	0.090
Gender	-	-	0.005
Male	114 (68.7)	25 (47.2)	-
Female	52 (31.3)	28 (52.8)	-
CCI, median (IQR)	3 (1-6)	3 (1-5)	0.104
Comorbidity	125 (75.3)	38 (71.7)	0.601
HT	65 (39.2)	23 (43.4)	0.584
Diabetes mellitus	44 (26.5)	22 (41.5)	0.038
CAD	31 (18.7)	10 (18.9)	0.975
CHF	18 (10.8)	6 (11.3)	0.923
SVD	16 (9.6)	1 (1.9)	0.051*
Demans	6 (3.6)	1 (1.9)	0.462*
COPD	16 (9.6)	13 (24.5)	0.005
Liver disease	7 (4.2)	1 (1.9)	0.383*
CKD	18 (10.8)	5 (9.4)	0.771
Malignancy	20 (12.0)	5 (9.4)	0.602
Other	16 (9.6)	4 (7.5)	0.442*

*Unless otherwise stated, results are n; given as %. BMI: Body mass index, CCI: Charlson comorbidity index, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, IQR: Interquartile range, SVD: Cerebrovascular disease, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease

Initial Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE IV, Simplified Acute Physiology Score III, and Sequential Organ Failure Assessment scores calculated after the ICU admission were similar in both groups. Considering the interventions performed in the ICU, the frequency of arterial and central venous catheters were found to be higher in patients with obesity ($p<0.05$). The frequency of hemodialysis, mechanical ventilation, and tracheostomy was similar in both groups. The frequency of treatments performed on both groups was similar. Complications that developed included the incidence of AKI that was higher in patients with obesity, and the rate of secondary infection was similar between the groups. Mechanical ventilation time and ICU stay were found to be higher in patients with obesity (Table 2). Mortality rates were similar in patients with obesity (n=83; 50%) and those without (n=27; 50.9%). The ROC analysis results that were performed to investigate the relationship between the BMI and mortality and determine a BMI value to predict mortality between the groups found no relationship between the BMI and mortality (AUC: 0.499) (Figure 1).

The laboratory parameter examined of patients with obesity and without obesity revealed that the laboratory parameters and blood gas values of patients were similar during admission. Ppeak was observed to be higher in patients with obesity in the mechanical ventilator parameters; however, their tidal volume was found to be lower ($p<0.05$). No difference was found in other mechanical ventilator parameters (Table 3).

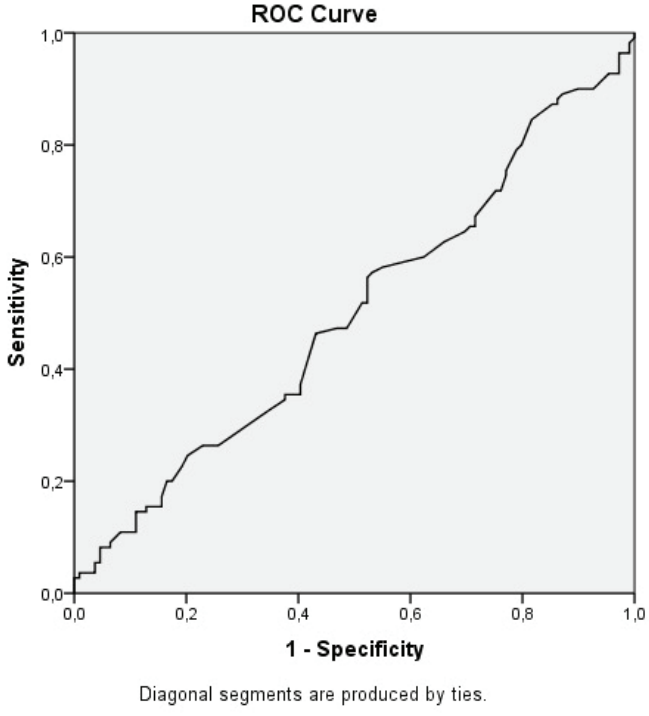

Figure 1. ROC analysis results for BMI and motility relationship (AUC: 0.499)
BMI: Body mass index, AUC: Area under curve, ROC: Receiver operating characteristic

Table 2. Intensive care scores of patient interventions and treatments

Parameters	Non-obese (n=166; 75.8%)	Obese (n=53; 24.2 %)	p
APACHE II, median (IQR)	22 (16-28)	21 (17-26)	0.530
APACHE IV, median (IQR)	64 (38-95)	63 (37-84)	0.659
SAPS III, median (IQR)	56 (42-72)	58 (50-69)	0.708
SOFA, median (IQR)	6 (2-9)	6 (3-11)	0.408
Initiatives			
Arterial catheter	147 (88.6)	52 (98.1)	0.035
Central venous catheter	130 (78.3)	48 (90.6)	0.046
Hemodialysis	45 (27.1)	15 (28.3)	0.865
Mechanical ventilation	128 (77.1)	46 (86.8)	0.129
Tracheostomy	23 (13.9)	7 (13.2)	0.905
Treatment			
Hydroxychloroquine	83 (50.0)	29 (54.7)	0.550
Favipiravir	118 (71.1)	41 (77.4)	0.373
Ritonavir/lopinavir	17 (10.2)	7 (13.2)	0.547
Tocilizumab	31 (18.7)	9 (17.0)	0.781
Steroid	38 (22.9)	12 (22.6)	0.970
Vasoactive agent	130 (78.3)	41 (77.4)	0.884
Antibiotic	154 (92.8)	50 (94.3)	0.487
Blood product	72 (43.4)	26 (49.1)	0.469
Secondary infection	84 (50.6)	26 (49.1)	0.845
AKI	107 (64.5)	42 (79.2)	0.044
Mechanical ventilation time, median (IQR)	5.6 (1.8-11.6)	10.3 (3.4-14.9)	0.017
ICU length of stay, median (IQR)	6.3 (2.6-14.8)	11.3 (6.0-17.3)	0.004
Mortality	83 (50.0)	27 (50.9)	0.905

*Unless otherwise stated, results are n; given as %. APACHE II: Acute physiology and chronic health assessment II, APACHE IV: Acute physiology and chronic health assessment iv, SAPS III: Simplified acute physiology score III, SOFA: Sepsis-related organ failure assessment, AKI: Acute kidney injury, ICU: Intensive care unit, IQR: Interquartile range

RESULT

Study results in the examination of the relationship between the BMI and mortality in patients who are followed up with the diagnosis of COVID-19 in the ICU found no relationship.

Table 3. Laboratory and clinical parameters of patients

Parameters	Non-obese (n=166; 75.8%)	Obese (n=53; 24.2%)	p
Lymphocyte count	0.75 (0.46-1.25)	0.67 (0.41-1.12)	0.305
Ferritin	529 (217-1164)	511 (178-1101)	0.817
Procalcitonin	0.94 (0.25-4.80)	0.64 (0.21-1.66)	0.218
CRP	152 (63-237)	145 (54-216)	0.438
Troponin	72 (17-245)	56 (14-167)	0.792
D-Dimer	1.85 (0.83-4.95)	1.89 (0.63-4.77)	0.365
Fibrinogen, (mean ± SD)	488±176	521±175	0.237
pH, (mean ± SD)	7.28±0.16	7.32±0.12	0.136
pO_2	65 (48-84)	65 (44-76)	0.343
pCO_2	38.1 (30.7-48.2)	36.8 (30.1-48.1)	0.841
Lactate	1.5 (1.1-1.9)	1.1 (1.0-1.9)	0.167
Glucose	156 (121-212)	153 (116-206)	0.654
ALT	29 (17-65)	30 (18-57)	0.947
AST	49 (29-89)	63 (25-125)	0.437
Sodium	137 (134-142)	137 (133-141)	0.567
Hemoglobin, (mean ± SD)	10.8±2.5	10.5±2.0	0.337
Hematocrit, (mean ± SD)	33.5±7.4	32.4±5.5	0.309
PLT	216 (150-298)	225 (171-297)	0.432
WBC	10.98 (7.86-16.35)	11.56 (7.38-16.53)	0.974
Respiratory Rate	25 (20-34)	27 (21-35)	0.272
Fever (mean ± SD)	36.9±1.1	36.9±1.4	0.890
PaO_2/FiO_2	144 (93-206)	112 (85-215)	0.433
FiO_2	60 (45-76)	50 (41-70)	0.359
PEEP	8 (7-9)	9 (7-10)	0.431
TV	507 (413-579)	445 (409-514)	0.029
Ppeak	20 (17-25)	25 (23-27)	0.048
WOBv	1.32 (1.19-1.54)	1.37 (1.09-1.58)	0.831

*Unless otherwise stated, results are n; given as %. CRP: C-reactive protein, pO_2: Partial oxygen pressure, pCO_2: Partial carbon dioxide pressure, ALT: Alanine Aminotransferase, AST: Aspartate aminotransferase, PLT: Platelet, WBC: White blood cell, PaO_2: Partial arterial oxygen pressure, FiO_2: Inspired fraction of oxygen exhaled, PEEP: Positive end-expiratory pressure, TV: Tidal volume, Ppeak: Inspiratory peak airway pressure, Pplato: Plateau pressure, WOBv: Work of breathing ventilator, SD: Standard deviation

DISCUSSION

Our research results revealed similar ICU scores and laboratory values; however, patients with obesity were concluded to have longer ICU stay and mechanical ventilation periods. In addition, patients with obesity were younger; however, their frequency of DM and COPD and incidence of AKI were higher.

Obesity is a common problem today and the number of obese individuals is expected to increase further in the coming years (18,19). Increased obesity was previously revealed in many comorbid diseases, including cardiovascular diseases and DM (20). Our research results show that our patients with obesity and COVID-19 are younger; however, their frequency of DM and COPD is higher. Our findings are compatible with the results in the literature. Previous studies on patients with COVID-19 revealed an increased BMI and the association of COPD and DM were common, which increase with the severity of the disease (21-23). The severity and mortality of COVID-19 were found to be associated with age, gender, and comorbidities, such as cardiovascular diseases and respiratory diseases, in similar studies (23-26). Individuals with comorbid diseases were observed to often have overexpression of the angiotensin-converting enzyme-2 (ACE-2) receptor (27). Severe Acute Respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infects the respiratory system, as well as other organs and systems in humans via attaching to the ACE-2 receptor in human cells after spike protein activation by transmembrane protease serine 2. This may explain the COVID-19 susceptibility of patients with obesity and comorbidities. Obesity and chronic inflammation are closely associated with proinflammatory activation and resulting endothelial dysfunction. Chronic inflammation in patients with obesity was estimated to contribute to the higher mortality due to increased inflammatory response to COVID-19 infection and impaired T-cell-induced immune response (28), which is characterized by obesity, adipose tissue remodeling, and proinflammatory changes in the adipokine profile (29,30). Obesity has been linked to an imbalance of pro- and anti-inflammatory adipokines, which has been linked to an increased risk of acute lung damage (30).

Our research results revealed that although the peak pressure was higher in patients with obesity who received mechanical ventilation support, they had lower tidal volumes. This situation can be explained by the effects of the increased adipose tissue on respiratory physiology. Patients with obesity have increased adipose tissue in the thoracic and abdominal walls that exerts extra pressure on the chest wall and diaphragm. Therefore, the diaphragm is

displaced toward the thorax and the lung volumes decrease (31). Patients with obesity are ventilated at higher pressures (32,33) during mechanical ventilation; however, they tend to have lower lung volume and functional residual capacity (34). In addition, due to venous stasis and reduced arterial perfusion, patients with obesity in the ICU are at risk for increased intra-abdominal pressure (35,36). Moreover, increased visceral fat accumulation in the abdominal area may increase the intra-abdominal pressure and cause an increased respiratory workload (32,33). Finally, obesity is a known risk factor for the development of acute respiratory distress syndrome (37,38).

Our research result found a longer duration of ICU stays in patients with obesity than those without obesity. Patients with obesity were previously seen with a longer ICU stay (39). Studies on patients with COVID-19 found that patients with obesity and COVID-19 have a longer hospitalization period, similar to our results (40,41) since patients with obesity are more susceptible to complications. Vascular problems are common in patients with obesity, and our study found a higher frequency of using arterial catheters and central venous catheters in these patients. This may lead to infection and catheter-related complications, thus prolonging the duration of the ICU stay. In addition, the incidence of pressure ulcers increases in patients with obesity due to the deterioration of tissue perfusion due to the increased adipose tissue (42). Our investigation found no difference in ICU mortality across the groups. No statistically detectable phenomena were found that linked fat individuals to higher ICU survival (42,43). Obesity is an independent risk factor for the development of AKI, which leads to prolonged ICU stay and increased mortality (44-46). Finally, nursing care becomes difficult in patients with obesity due to the large body surface area. This may lengthen the ICU follow-up period by increasing complications such as skin laceration and infection (47).

Our investigation found no difference in ICU mortality across the groups. The phenomenon that associated obese patients with better survival in the ICU could not be statistically detected. In the ROC analysis carried out to find a cut-off value for which BMI could be associated with mortality, no significant results could be obtained. Obesity is a risk factor for morbidity and death owing to SARS-CoV-2 infection, regardless of its connection with other comorbidities, according to previous research (48,49). Some studies have suggested that it has no effect on patient outcomes, which is consistent with our results (50). This may be related to the younger age of patients with obesity. In addition, the presence of patients with multiple types of obesity in the ICU and the differences in patients with obesity may affect the results. Patients with obesity vary according to obesity classes and comorbid disease burdens. Given these previous findings in patients with obesity and COVID-19, patients with and without obesity in our critically ill cohort had similar disease severity and mortality. Obesity appears to be a risk factor for serious disease in COVID-19; however, our findings show that individuals with obesity, who become critically sick, have inflammatory profiles comparable to those who are not.

Study Limitations

In addition to the strengths of our research, such as preventing data loss using an electronic query of the clinical decision support system and completing all treatment processes of the patients in our center, our research also has some limitations. First, the retrospective study design may pose a risk of bias that may affect the results. Having a single-centered population prevents the generalization of results. Patients with obesity were younger than those without obesity in our sample has the potential to affect the results. The lack of other data to support obesity defined by BMI, such as waist circumference and waist-hip ratio, may have influenced the accuracy of the groups created using BMI. Insufficient records of administered diuretic or fluid therapy before the ICU admission may have affected the BMI and AMI data by changing the weight and urine amount of patients that was measured in the ICU.

CONCLUSION

Patients with obesity followed up in the ICU with COVID-19 diagnosis have longer periods of ICU stay and mechanical ventilation. In addition, patients with obesity are younger and their frequency of DM and COPD is also higher. The incidence of AKI increases in patients with obesity. However, no association was found between obesity and mortality.

ETHICS

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital of Local Ethics Committee (number: 2021/413).

Informed Consent: Written informed consent was obtained from the patients and their relatives.

Authorship Contributions

Surgical and Medical Practices: D.A., R.Y., N.S.E., Concept: D.A., R.Y., N.S.E., Design: D.A., R.Y., N.S.E., Data Collection or Processing: D.A., N.S.E., Analysis or Interpretation: D.A., Literature Search: D.A., R.Y., N.S.E., Writing: D.A., R.Y., N.S.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. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Geneva, Switzerland: World Health Organization; 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264-6.
3. Li M, Dong Y, Wang H, Guo W, Hu D, Guo W, et al. Cardiovascular disease potentially contributes to the progression and poor prognosis of covid-19. Nutr Metab Cardiovasc Dis 2020;30:1061-7.
4. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ, et al. Association of Cardiovascular Disease With Coronavirus Disease 2019 (COVID-19) Severity: A Meta-Analysis. Curr Probl Cardiol 2020;45:100617.
5. Mantovani A, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. Nutr Metab Cardiovasc Dis 2020;30:1236-8.
6. Ekiz T, Pazarlı AC. Relationship between COVID-19 and obesity. Diabetes Metab Syndr 2020;14:761-3.
7. Hussain A, Vasas P, El-Hasani S. Letter to the Editor: Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism 2020;108:154256.
8. Yates T, Razieh C, Zaccardi F, Rowlands AV, Seidu S, Davies MJ, et al. Obesity, walking pace and risk of severe COVID-19 and mortality: analysis of UK Biobank. Int J Obes (Lond) 2021;45:1155-9.
9. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism 2020;108:154262.
10. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723-7.
11. Marik P, Varon J. The obese patient in the ICU. Chest 1998;113:492-8.
12. Macha M, Molina EJ, Franco M, Luyun L, Gaughan JP, McClurken JB, et al. Pre-transplant obesity in heart transplantation: are there predictors of worse outcomes? Scand Cardiovasc J 2009;43:304-10.
13. Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: A systematic review and meta-analysis. J Med Virol 2021;93:257-61.
14. Du Y, Lv Y, Zha W, Zhou N, Hong X. Association of body mass index (BMI) with critical COVID-19 and in-hospital mortality: A dose-response meta-analysis. Metabolism 2021;117:154373.
15. Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020;75:1742-52.
16. Kooistra EJ, Brinkman S, van der Voort PHJ, de Keizer NF, Dongelmans DA, Kox M, et al. Body Mass Index and Mortality in Coronavirus Disease 2019 and Other Diseases: A Cohort Study in 35,506 ICU Patients. Crit Care Med 2021 Jul 16.
17. https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html
18. WHO - World Health Organization. Obesity and overweight 2010. Updated June 2016.
19. EASO - European Association for the Study of Obesity: Obesity facts and figures. Available from: URL: http:// easo.org/education-portal/obesity-facts-figures/
20. Andersen CJ, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity. Adv Nutr 2016;7:66-75.
21. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. Clin Infect Dis 2020;71:896-7.
22. Huang R, Zhu L, Xue L, Liu L, Yan X, Wang J, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu province, China: A retrospective, multi-center study. PLoS Negl Trop Dis 2020;14:e0008280.
23. Sabaz MS, Özdemir F, Özakin O, Türkmen ÜA, Dinç V. Intensive Care Unit Admission Parameters for Patients with COVID-19. Med J Bakirkoy 2021;17:254-61.
24. Erol AT, Aşar S, Ören Bilgin B, Çukurova Z, Sabaz MS. Risk Factors for 28-day Mortality Among COVID-19 Patients in an Intensive Care Unit of a Tertiary Care Center in Istanbul. Med J Bakirkoy 2021;17:100-7.
25. Imam Z, Odish F, Gill I, O'Connor D, Armstrong J, Vanood A, et al. Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med 2020;288:469-76.
26. Sabaz MS, Aşar S. Association of Charlson Comorbidity and Pneumonia Severity Indices with Mortality in Patients with Coronavirus Disease-2019 in the Intensive Care Unit. Turk J Intensive Care 2021;19:33-41.
27. Tuty Kuswardhani RA, Henrina J, Pranata R, Anthonius Lim M, Lawrensia S, Suastika K. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Metab Syndr 2020;14:2103-9.
28. Chiappetta S, Sharma AM, Bottino V, Stier C. COVID-19 and the role of chronic inflammation in patients with obesity. Int J Obes (Lond) 2020;44:1790-2.
29. Heinonen S, Saarinen L, Naukkarinen J, Rodríguez A, Frühbeck G, Hakkarainen A, et al. Adipocyte morphology and implications for metabolic derangements in acquired obesity. Int J Obes (Lond) 2014;38:1423-31.
30. Leal Vde O, Mafra D. Adipokines in obesity. Clin Chim Acta 2013;419:87-94.
31. Koenig SM. Pulmonary complications of obesity. Am J Med Sci 2001;321:249-79.
32. Pépin JL, Borel JC, Janssens JP. Obesity hypoventilation syndrome: an underdiagnosed and undertreated condition. Am J Respir Crit Care Med 2012;186:1205-7.
33. Chlif M, Keochkerian D, Choquet D, Vaidie A, Ahmaidi S. Effects of obesity on breathing pattern, ventilatory neural drive and mechanics. Respir Physiol Neurobiol 2009;168:198-202.
34. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. J Appl Physiol (1985) 2010;108:206-11.
35. Kim IB, Prowle J, Baldwin I, Bellomo R. Incidence, risk factors and outcome associations of intra-abdominal hypertension in critically ill patients. Anaesth Intensive Care 2012;40:79-89.
36. Aşar S, Kucur Tülübaş E, Sabaz MS, Acicbe Ö. The Effect of PEEP Adjusted by Automatic Recruitment Maneuver on Total and Dynamic Mechanical Power in Bariatric Surgery. Med J Bakirkoy 2021;17:262-7.

37. Gong MN, Bajwa EK, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. Thorax 2010;65:44-50.
38. Asar S, Acicbe Ö, Sabaz MS, Tontu F, Canan E, Cukurova Z, et al. Comparison of Respiratory and Hemodynamic Parameters of COVID-19 and Non-COVID-19 ARDS Patients. Indian J Crit Care Med 2021;25:704-8.
39. Sabaz MS, Aşar S. Identification of Factors Associated with Prolonged Stay in the Intensive Care Unit. Med J Bakirkoy 2021;17:233-42.
40. Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet 2020;395:1544-15.
41. Gao F, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, et al. Obesity Is a Risk Factor for Greater COVID-19 Severity. Diabetes Care 2020;43:e72-4.
42. Dolgun E, Yavuz M. Aşırı şişmanlık cerrahisinde hemşirelik bakımı. (Nursing Care in Morbid Obesity Surgery). Maltepe Üniversitesi Hemşirelik Bilim ve Sanatı Dergisi 2010;3:85-92.
43. Terekeci H, Kucukardali Y, Top C, Onem Y, Celik S, Oktenli C. Risk assessment study of the pressure ulcers in intensive care unit patients. Eur J Intern Med 2009;20:394-7.
44. Sabaz MS, Aşar S, Sertçakacılar G, Sabaz N, Çukurova Z, Hergünsel GO. The effect of body mass index on the development of acute kidney injury and mortality in intensive care unit: is obesity paradox valid? Ren Fail 2021;43:543-55.
45. Hergünsel GO, Sabaz MS. The effect of obesıty on mortalıty ın gerıatrıc patıents followed ın the ıntensıve care unıt. Turkish Journal of Geriatrics 2021;24:315-29.
46. Sabaz MS, Çetingök H, Sertcakacilar G, Yener YZ, Atiç E, Erbahceci Salik A, et al. Monitorization of NGAL, Creatinine and Renal Blood Flow in the Follow-up of Acute Kidney Injury in Intensive Care. Med J Bakirkoy 2021;17:85-93.
47. Winkelman C, Maloney B, Kloos J. The impact of obesity on critical care resource use and outcomes. Crit Care Nurs Clin North Am 2009;21:403-22.
48. Frank RC, Mendez SR, Stevenson EK, Guseh JS, Chung M, Silverman MG. Obesity and the Risk of Intubation or Death in Patients With Coronavirus Disease 2019. Crit Care Med 2020;48:e1097-101.
49. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. Ann Intern Med 2020;173:773-81.
50. Wolf M, Alladina J, Navarrete-Welton A, Shoults B, Brait K, Ziehr D, et al. Obesity and Critical Illness in COVID-19: Respiratory Pathophysiology. Obesity (Silver Spring) 2021;29:870-8.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:400-406
DOI: 10.4274/BMJ.galenos.2021.2021.10-16

Research

Satisfaction, Perspective, and Attitude Toward E-learning among Emergency Medicine Physicians

Acil Tıp Hekimlerinin E-öğrenmeye Yönelik Memnuniyetleri, Bakış Açıları ve Tutumları

Göksu Bozdereli Berikol, Buğra İlhan, Halil Doğan

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Emergency Medicine, Istanbul, Turkey

ABSTRACT

Objective: E-learning gained popularity since the sudden pandemic entry, which revealed the need to adapt to our practice after becoming mandatory. Thus, this study aimed to investigate the perceptions toward e-learning among emergency medicine physicians.

Methods: In this questionnaire-based cross-sectional study, an online questionnaire was given about demographics, self-efficacy, satisfaction, self-control, anxiety, perceived usefulness, and attitudes toward e-learning was conducted on emergency medicine residents and specialists who are remotely involved in emergency medicine training in their departments due to the pandemic. The self-efficacy, satisfaction, interactivity, perceived ease of use, perceived benefit, self-control, and attitude scores were calculated based on the total Likert points of statements, and correlations were analyzed.

Results: This study included 74 participants who remotely performed emergency medicine training during the study. Experience in years showed statistically higher satisfaction (p=0.018), self-control (p=0.003), ease of use (p=0.042), perception of benefit (p=0.022), and attitude (p=0.030) rates in residents. Experienced participants has a statistically lower self-efficacy (p=0.044) and higher perception of ease of use (p=0.034). Perception of benefit (p=0.009), self-control (p=0.006), perception of ease of use (p=0.01), and attitude (p=0.018) was statistically higher in high computer skill levels. Perception of benefit (r=0.543) is associated with higher computer skill levels, satisfaction (r=0.407), and perception of interactivity (r=0.498). Satisfaction had a positive correlation with self-control (r=0.543, p=0.000) and benefit perception (r=0.543, p=0.000).

Conclusion: Increased interaction, improved users' computer skills and maintained higher self-efficacy and benefit perception are important to increase the satisfaction and adoption with e-learning.

Keywords: E-learning, emergency medicine, distance learning, satisfaction

ÖZ

Amaç: E-öğrenme, pandeminin girişinden bu yana popülerlik kazandı. Zorunlu hale geldiğinde, pratiğe uyum sağlama ihtiyacını da ortaya çıkardı. Çalışmamız acil tıp hekimlerinin e-öğrenmeye yönelik algılarını araştırmayı amaçlamıştır.

Gereç ve Yöntem: Bu kesitsel anket çalışması süresince pandemi nedeni ile acil tıp eğitimini kliniklerinde uzaktan eğitim uygulayan acil tıp asistanları ve acil tıp uzmanlarına öz yeterlilik, memnuniyet, öz kontrol, kaygı, algılanan fayda ve e-öğrenmeye yönelik tutumlarla ilgili bir anket uygulandı. İfadelerin toplam Likert puanlarına göre öz yeterlik, memnuniyet, interaktivite, kullanım kolaylığı algısı, fayda algısı, öz kontrol ve tutum puanları hesaplanmış ve korelasyonları analiz edilmiştir.

Bulgular: Çalışma süresince acil tıp eğitimini uzaktan gerçekleştiren 74 katılımcı çalışmaya dahil edildi. Yıllara göre deneyim, asistanlarda istatistiksel olarak daha yüksek memnuniyet (p=0,018), kendini kontrol (p=0,003), kullanım kolaylığı (p=0,042), fayda algısı (p=0,022) ve tutum (p=0,030) göstermiştir. Deneyimli katılımcılar istatistiksel olarak daha düşük öz-yeterlik (p=0,044) ve daha yüksek kullanım kolaylığı algısı (p=0,034) idi. Fayda algısı (p=0,009), özdenetim (p=0,006), kullanım kolaylığı algısı (p=0.01), tutum (p=0.018) yüksek bilgisayar beceri düzeylerinde istatistiksel olarak daha yüksekti. Fayda algısı (r=0,543) daha yüksek bilgisayar beceri seviyeleri ile ilişkilidir; memnuniyet (r=0,407) ve etkileşim algısı (r=0,498). Memnuniyet ile öz kontrol (r=0,543, p=0,000) ve fayda algısı (r=0,543, p=0,000) arasında pozitif bir ilişki vardı.

Sonuç: Memnuniyeti ve e-öğrenmeye uyumu artırmak için etkileşimi artırmak, kullanıcıların bilgisayar becerilerini geliştirmek ve daha yüksek öz-yeterlik ve fayda algısını sürdürmek önemlidir.

Anahtar Kelimeler: E-öğrenme, acil tıp, uzaktan öğrenme, memnuniyet

Address for Correspondence: Göksu Bozdereli Berikol, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Emergency Medicine, Istanbul, Turkey
Phone: +90 553 480 33 84 E-mail: gokxsu@hotmail.com ORCID ID: orcid.org/0000-0002-4529-3578

Cite as: Bozdereli Berikol G, İlhan B, Doğan H. Satisfaction, Perspective, and Attitude Toward E-learning among Emergency Medicine Physicians. Med J Bakirkoy 2021;17:400-406

Received: 25.10.2021
Accepted: 2.12.2021

INTRODUCTION

Distance education is a form of education that brings students, teachers, and course resources together in different places using technology, which enables communication among them (1). With today's technologies, education is carried to different platforms online or offline, simultaneous, or independent of time. It has been used with names, such as online, e-learning, web-based learning, and virtual learning. This concept, which was first introduced in 1892 at the University of Wisconsin of the United States, was firstly used in our country in 1956 (2).

Theoretical Framework

User's perceptions and attitudes toward e-learning technologies are essential in the success of the educational process (3). Self-efficacy and satisfaction have a role in the achievement and motivational mechanisms (4). User satisfaction is defined as the point where competence is sought, wherein satisfaction is "the state of being above an expectation level that is expressed by the user" (5). Bandura's Social Cognitive Theory defined self-efficacy as "an individual's belief in his or her own ability to organize and implement action to produce the desired achievements and results" (4,6). The other factors that affect the acceptance of technology include perceived benefit and ease of use. Leung referred to perceived benefit as "the perception of the positive consequences that are caused by a specific action" (7), whereas perceived ease of use is defined as "the degree to which a person believes that using a particular system would be free of effort" (8). The standardized scales are developed to measure these perceptions and factors for technology acceptance (2,3,8-11).

The Specialization Board of Medicine in Turkey by 2017 in the Emergency Medicine Residency Training Core Curriculum recommends at least 4 h per week of education offered in the department, 4 h practical (per patient visit is like a simulation laboratory) at least monthly with the need to include education and trainers. Training of 2 h should be given under the supervision of an educator or emergency medicine specialist.

During the Coronavirus disease-2019 (COVID-19) outbreak, service provision increased in hospitals and emergency departments. Concurrently, improvement in the face-to-face theoretical training for emergency and residents working in the emergency department has become necessary due to social isolation and contact and limited residency training duration, thus deficiencies were tried to be remedied by distance education (12,13). This study aimed to determine the satisfaction level of emergency physicians with the learning model in distance education and the factors that affect their satisfaction levels. Additionally, the study will guide the efforts to eliminate the factors that cause dissatisfaction and avoid disruption of the continuity of residency training in pandemic circumstances.

METHODS

Study Design

The study University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital questionnaire-based cross-sectional study that was conducted between June 6, 2020, and August 25, 2020, after approval from the local ethics committee (2020/270).

Population

Maximum diversity sampling is aimed at our study, which was conducted with emergency physicians (emergency medicine residents and specialists) who experienced e-learning in their departments of different ages and experiences. Emergency medicine specialists who work in institutions that do not provide specialty training or who do not participate in department training or those who refuse to participate in the survey were excluded from the study.

Google forms were used due to the social distance precautions in the pandemic. The questionnaire form was delivered to the participants via emergency medical associations' mail groups and social media groups. The questionnaire form was sent to emergency medicine departments (n=308) that provide distance education, wherein 79 responded. A total of 74 responses were included in the analysis, excluding five physicians who only provided emergency medical training to staff or students (interns, nurses, and paramedics) other than emergency medicine residents. Consent information was taken from all participants.

Data Collection

Our study chose the online survey method since it provides an easy way to access departments and clinics that started e-learning during the pandemic.

The questionnaire form consists of structured questions, which were prepared based on Likert's 5-level answers as "strongly agree," "agree," "neither agree nor disagree," "disagree," and "strongly disagree."

Since they have not been studied before in the population with emergency medicine training, the scale framework questions were designed in the previously analyzed studies for reliability and validity (2,3,9). The questionnaire form was sent to 20 emergency medicine residents for a pilot

study, and incomprehensible and misunderstood erroneous questions were corrected with the feedbacks. Responses and participants were not involved in the study analysis.

The questionnaire form consists of 3 parts. The contents of the questions in the sections are given below:

Section 1

A- Demographic characteristics (gender, age, title, marital status, number of children, and tenure)

B1- Computer usage knowledge level

B2- Distance education knowledge levels (presence of experience and environment)

Section 2

C1- Self-efficacy levels (using distance education, management, and content management)

C2- Perception of Anxiety (mood characteristics of distance education on the person)

C3- Perception of Interactivity (perceptions about interactions during distance education)

C4- Satisfaction perceptions (distance education module, course content, and interactions)

C5- Benefit perceptions (benefits of distance education and their thoughts on its future use)

C6- Self-control perceptions (self-learning and usability)

C7- Perception of ease of use of the system

Section 3

C8- General views and attitudes

These statements are shown in the Supplementary document.

Self-efficacy, anxiety, satisfaction, utility perception, ease of use, and attitude scores are calculated with total Likert points of questions (raw) for each score. Every question has a minimum point of 1 and a maximum of 5. Afterward, the median interquartile range (IQR) was analyzed for each score.

Statistical Analysis

Numerical variables were represented as mean ± standard deviation or median (IQR). Attribute variables were shown with numbers and percentages. The Shapiro-Wilks and Kolmogorov-Smirnov tests determined the distribution of the groups. The self-efficacy, satisfaction, interactivity, ease of use perception, benefit perception, self-control, and attitude scores were calculated based on the total 5-level Likert points. For each score, independent groups were evaluated using the independent t-test, the Mann-Whitney U test, and the Kruskal-Wallis tests. The relationship between attribute variables was evaluated using the chi-square test. The Spearman test and partial correlations were used in the correlation analysis according to data distribution. The Statistical Package for the Social Sciences® for Windows version 23.0 program was used for statistical analysis. Statistical significance level was accepted as p-values of <0.05.

RESULTS

Reliability Analysis

The reliability analysis result of the statements made revealed a >0.90 (0.965) Cronbach's alpha coefficient (Table 1).

Expressions C102, C104, C83, and c100 were excluded from the analysis due to loading on more than one factor. Kaiser-Meyer-Olkin (KMO and Bartlett's test) test was 0.716 ($p<0.001$)

This study included 74 participants, with a median age of 30 years (IQR=5), wherein 44 (59.5%) were males and 30 (40.5%) were females. The median (IQR) of each total score and the descriptive data of participant demographics are shown in Table 2. No statistical difference was found between the groups in terms of gender, title, marital status, and the number of children regarding the scores in self-efficacy, Satisfaction, Interactivity, Perception of Benefit, Self-control, Ease of use perception, Anxiety, and Attitude ($p>0.05$, Mann-Whitney U).

Experience in years showed statistically higher satisfaction ($p=0.018$), self-control ($p=0.003$), ease of use ($p=0.042$), benefit perception ($p=0.022$), and attitude ($p=0.030$) rates in residents. However, experience in years is not statistically

Table 1. Reliability analysis for statements and categories

	Cronbach's alpha	Variance	Standard deviation	Mean
Self-efficacy (C1)	0.947	21.884	4.678	12.92
Anxiety (C2)	0.932	25.094	5.009	9.69
Interactivity (C3)	0.909	34.135	5.843	16.31
Satisfaction (C4)	0.931	24.978	4.998	13.62
Perception of benefit (C5)	0.972	59.123	7.689	21
Self-regulation (C6)	0.953	37.458	6.120	16.53
Ease of use (C7)	0.972	31.343	5.599	13.16
General views and attitudes (C8)	0.947	494.661	22.241	76.45

Table 2. Demographical data and scores of the participants

	n=74	n (%)
Age (median ± SD)	30 (IQR=5)	
Gender	Female	30 (40.5%)
	Male	44 (59.5%)
Marital status	Single	36 (48.6%)
	Married	38 (68.9%)
Children	0	51 (31.1%)
	1	23 (30.8%)
Institute	University	34 (72.3%)
	Training and research hospital	13 (27.7%)
Degree	Resident	55 (74.3%)
	Specialist	19 (25.7%)
EM residency year	0-12 m	10 (17.9%)
	13-24 m	12 (21.4%)
	25-36 m	10 (17.9%)
	37-48 m	16 (28.6%)
	48 m+	8 (14.3%)
Experience as specialist	0-2 years	1 (4.8%)
	3-4 years	6 (28.6%)
	5-8 years	8 (38.1%)
	9+	6 (28.6%)
Computer Use Skills	Beginner	6 (8.1%)
	Medium	35 (47.3%)
	Very Good	11 (14.9%)
	Advanced	22 (29.7%)
E-learning experience	No	34 (51.4%)
	Yes Listened Presented Both	40 (48.6%) 28 (37.8) 2 (2.7%) 10 (13.5%)
Following the lectures	Yes No Sometimes	44 (59.5%) 2 (2.7%) 28 (37.8%)
Offline use	Yes No	15 (20.3%) 59 (79.7%)
Score	Median (IQR)	
Self-efficacy score	12/ (IQR=9)	
Anxiety score	10 (IQR=11)	
Satisfaction score	12 IQR=12)	
Perception of utility score	18 (IQR=15.50)	
Ease of use score	11 (IQR=12)	
Attitude score	61.5 (IQR=33.25)	

IQR: Interquartile range, SD: Standard deviation

significant regarding the scores in specialists (p>0.05, Kruskal-Wallis).

The rate of previous distance education experience was 48.6% (n=40). Participants experienced a statistically lower self-efficacy in e-learning (p=0.044) and higher ease of use perception (p=0.034). Experience in e-learning is not statistically significant among the groups regarding satisfaction (p=0.059).

Considering the computer use skills, participants in beginner and medium levels (low computer use skills) were 41 (55.4%), whereas 33 (44.6%) in very good and advanced (high computer use skills) levels. Self-efficacy (p=0.960), interactivity (p=0.096), satisfaction (p=0.051), and anxiety (p=0.361) scores were not different between low and high computer use skills. Benefit perception (p=0.009), self-control (p=0.006), ease of use perception (p=0.01), and attitude (p=0.018) was statistically higher in high computer skill levels.

The most commonly used distance education portal was Zoom (n=53, 85%) followed by GoToMeeting (n=9, 14.1%), Skype (n=9, 14.1%), Microsoft Teams (n=5, 7.9%), Moodle (n=2, 3.1%), and others. Majority of the users learned the distance education portals while using (n=40, 63.5%), followed by friends and colleagues (n=23, 36.5%), and via internet and videos (n=19, 30.2%).

In addition to emergency medicine residency training, the trainees were 6th-grade medical students (n=6, 22.2%) and other health personnel (nurse, paramedic, and undergraduate students) (n=5, 18.5%).

The places where the participants followed the distance education were home (n=71, 95.9%), hospital (n=44, 59.5%), vehicle (n=20, 27%), and other (n=10, 13.5%), respectively.

The rate of following the lessons with distance education was 60.2%, of whom 73.2% (n=52) listened carefully to all the lessons, 8.5% (n=6) pretended to listen, and 31% (n=22) appeared online but deal with other things.

The most common reason for not attending the course was because of duty and post-seizure (83.9% and 51.6%, respectively). Only 20.3% of the lessons not attended have listened offline.

The most appropriate course time was chosen between 08.00-12.00 and 13.30-17.00 by the participants (36.4% and 33.8%, respectively). The majority of participants preferred the lesson duration to be between 20-40 min (41.9%). The choice of lesson hours that can be rested daily mainly was 2 (58.1%) and 3 (24.3). The proportion of those who wanted

their education to be remote in the other year was 79.7%. The preferred frequency of distance education was mostly (60.9%) once a week.

Correlation Analysis

Correlation Analysis is shown in Table 3.

- Self-control has also shown a high degree of positive correlation [r=0.840, 95% confidence interval (CI): 0.754-0.898] with the perception of benefit.
- Attitudes showed a high positive correlation with ease of use perception (r=0.728, 95% CI: 0.595-0.823).
- Self-efficacy showed medium positive correlation with interactivity (r=0.498), satisfaction (r=0.407) and perception of benefit (r=0.415, 95% CI: 0.199-0.592).
- There is a very high degree positive correlation between satisfaction and self-control (r=0.796) and perception of benefit (r=0.861, 95% CI: 0.784-0.911). Satisfaction has a positive correlation with self-control (r=0.543, p=0.000, partial correlation) and perception of benefit (r=0.543, p=0.000, partial correlation).

DISCUSSION

Our study revealed that perceptions, such as self-efficacy, Satisfaction, Interactivity, Benefit, Self-control, Ease of use, Anxiety, and Attitude, were examined in participants who experienced distance learning in emergency medicine education.

As a result, third and fourth-year residents were highly satisfied with distance education. Satisfaction scores were not affected by the institution, title, gender, and marital status.

Our study revealed no significant difference between the institutions in terms of self-efficacy in distance education. Therefore, all institutions that provide emergency medicine residency training are suitable for distance education.

Our study revealed that emergency physicians were satisfied with the content and functions of distance education and the multimedia environment. A study in medical students, nurses, and paramedics who received emergency medicine education divided the satisfaction into three groups: video, interactive video, and non-animated training, conducted a satisfaction survey with "before and after" questionnaires

Table 3. Spearman correlation analysis of sections

		Self-efficacy	Anxiety	Interactivity	Satisfaction	Perception of benefit	Self-control	Ease of use	Attitudes
Self-Efficacy	rho	1	-	-	-	-	-	-	-
		-	-	-	-	-	-	-	-
Anxiety	rho	-0.244*	1	-	-	-	-	-	-
	p	0.036	-	-	-	-	-	-	-
Interactivity	rho	0.498**	-0.361**	1	-	-	-	-	-
	p	0.000	0.002	-	-	-	-	-	-
Satisfaction	rho	0.407**	-0.324**	0.421**	1	-	-	-	-
	p	0.000	0.005	0.000	-	-	-	-	-
Perception of benefit	rho	0.415**	-0.291*	0.531**	0.861**	1	-	-	-
	p	0.000	0.012	0.000	0.000	-	-	-	-
Self-control	rho	0.397**	-0.351**	0.439**	0.796**	0.840**	1	-	-
	p	0.000	0.002	0.000	0.000	0.000	-	-	-
Ease of Use	rho	0.290**	-0.314**	0.486**	0.434**	0.549**	0.458**	1	-
	p	0.012	0.007	0.000	0.000	0.000	0.000	-	-
Attitudes	rho	0.192	-0.241*	0.550**	0.550**	0.612**	0.594**	**0.728****	1
	p	0.102	0.039	0.000	0.000	0.000	0.000	0.000	-

*Correlation is significant at 0.05 level, **Correlation is significant at 0.01 level

and revealed a high satisfaction in all groups (14). Thus, distance education can be an alternative to face-to-face in terms of theoretical training.

After the web-based preparation of the emergency medicine residency curriculum, a 1-year follow-up and satisfaction study revealed that 83% of emergency medicine residents were satisfied despite technical difficulties (15). Participation has increased compared to the previous year; however, no comparison was made in our study in the participation with previous years. Additionally, the high levels of satisfaction suggest that the online education model may be included in our education system in the future although it is still in its initial stage. Another indication of their satisfaction with the online training is that most participants (79.7%) want the online training to continue.

Participants experienced a statistically lower self-efficacy ($p=0.044$) and higher ease of use perception ($p=0.034$) in e-learning. Compatible with the literature, higher self-efficacy results with decreased experience can be explained by the Dunning Kruger effect (16). This effect is called the inability to acknowledge the individual lack of competence.

Distance education satisfaction studies regarding emergency medicine are limited in the literature. Mueller et al. (17) has presented their online academic emergency medicine experiences during the COVID-19 pandemic and reported that 80% of courses were conducted successfully. Nevertheless, online education satisfaction has not been included in the study.

Ease of use associated with experience and computer use skills also positively correlates with attitudes toward e-learning. We found that self-control and benefit perception are correlated with satisfaction.

Easy accessibility of distance education has shown a numerically higher level of satisfaction for married couples and participants with children. This situation was also revealed in a study conducted on nurses' satisfaction levels with distance education (9). Our study revealed high rates in married and those with children satisfaction levels. Similar results were obtained in the study conducted by Xing et al. (9) on nurses, which suggests that especially advanced-age peer training can also be provided on online platforms.

Marital status and social responsibilities in having children may cause disruptions in face-to-face education participation and following the lessons from time to time. Our study concluded that having a child and marital status did not affect following online classes. Therefore, online training is more acceptable and traceable in social life.

Additionally, our study received feedback from the participants about the time, frequency, and online training duration, which help in planning optimum online training.

Our study is the first to evaluate online education in emergency medicine residency training, thus we believe it will be a resource for future training and studies.

Study Limitations

The study included 2 months during the epidemic period. Distance education experiences may have been chosen or started as mandatory and acutely due to the epidemic since it is unclear whether the preparation, distance education portal training, training delivery, and a necessary separate curriculum may affect the satisfaction levels. Under normal circumstances, measurements can be repeated. Another study limitation was the different e-learning platforms. Thus, future studies may investigate the differences among the e-learning platforms regarding software used, quality of internet connection, duration of lessons, the experience of speakers, etc. The study was conducted during the COVID-19 pandemic, thus the low number of distance education clinics may have caused the return of the survey due to the low number of participants and the intensity of the pandemic conditions.

CONCLUSION

Increasing self-efficacy correlates with benefit perception, associated with higher computer skill levels, satisfaction, and interactivity perception. Increasing the interactivity, advancing user computer skills, augmenting the experience to maintain higher self-efficacy and benefit perception, and increasing satisfaction and adaptation of trainees to e-learning in mandatory conditions pandemic is essential. This study will elucidate the perceptions of distance education that affect attendance and patient care quality for further studies.

ETHICS

Ethics Committee Approval: The study University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital questionnaire-based cross-sectional study that was conducted between June 6, 2020, and August 25, 2020, after approval from the local ethics committee (2020/270).

Informed Consent: Consent information was taken from all participants.

Authorship Contributions

Concept: G.B.B., H.D., Design: G.B.B., B.İ., Data Collection or Processing: G.B.B., B.İ., Analysis or Interpretation: G.B.B., B.İ., Literature Search: G.B.B., Writing: G.B.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. Moore JL, Dickson-Deane C, Galyen K. e-Learning, online learning, and distance learning environments: Are they the same? The Internet and Higher Education 2011;14:129-35.
2. Begi˙mbetova K. Uzaktan eğitimde öğretim elemanı ve öğrencilerin memnuniyet düzeyi. Ankara: Gazi Üniversitesi, Bilişim Enstitüsü, Yönetim Bilişim Enstitüsü Anabilim Dalı, Yayınlanmamış Yüksek Lisans Tezi Ankara; 2015.
3. Isik O. E-learning satisfaction factors. Dans: Proceedings of the 39th Annual Meeting of the Decision Sciences Institute; 2008.
4. Doménech-Betoret F, Abellán-Roselló L, Gómez-Artiga A. Self-Efficacy, Satisfaction, and Academic Achievement: The Mediator Role of Students' Expectancy-Value Beliefs. Front Psychol 2017;8:1193.
5. Oliver RL. Satisfaction: a behavioral perspective on the consumer. 2nd ed. Armonk NY: M.E. Sharpe; 2010.
6. Bandura A. Self-efficacy: the exercise of control. New York: W.H. Freeman; 1997.
7. Leung Y. Perceived Benefits. In: Gellman MD, Turner JR, editors. Encyclopedia of Behavioral Medicine. New York, NY: Springer New York; 2013.
8. Davis FD. Perceived Usefulness, Perceived Ease of Use, and User Acceptance of Information Technology. MIS Quarterly 1989;13:319-40.
9. Xing W, Ao L, Xiao H, Liang L. Chinese Nurses' Preferences for and Attitudes About e-Learning in Continuing Education: A Correlational Study. J Contin Educ Nurs 2020;51:87-96.
10. Ilgaz H, Aşkar P. The Contribution of Technology Acceptance and Community Feeling to Learner Satisfaction in Distance Education. Procedia-Social and Behavioral Sciences 2013;106:2671-80.
11. Strong R. Investigating Students' Satisfaction with eLearning Courses: The Effect of Learning Environment and Social Presence. Journal of Agricultural Education 2012;53:98-110.
12. Pek JH, Low JWM, Lau TP, Gan HN, Phua DH. Emergency medicine residency training during COVID-19. Singapore Med 2020. DOI: 10.11622/smedj.2020139
13. Mufti A, Maliyar K, Sachdeva M, Doiron P. Modifications to dermatology residency education during the COVID-19 pandemic. J Am Acad Dermatol 2020;83:235-6.
14. Leszczyński P, Gotlib J, Kopański Z, Wejnarski A, Świeżewski S, Gałązkowski R. Analysis of Web-based learning methods in emergency medicine: randomized controlled trial. Arch Med Sci 2018;14:687-94.
15. Kornegay JG, Leone KA, Wallner C, Hansen M, Yarris LM. Development and implementation of an asynchronous emergency medicine residency curriculum using a web-based platform. Intern Emerg Med 2016;11:1115-20.
16. Zawadka M, Graczyńska A, Janiszewska A, Ostrowski A, Michałowski M, Rykowski M, et al. Lessons Learned from a Study of the Integration of a Point-of-Care Ultrasound Course into the Undergraduate Medical School Curriculum. Med Sci Monit 2019;25:4104-9.
17. Mueller M, Schriefl C, Holzer M, Roeggla M, Laggner AN, Ettl F. Education in Academic Emergency Medicine During the COVID-19 Pandemic - Our Experience From an Ongoing Crisis. Front Public Health 2020;8:592503.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:407-411
DOI: 10.4274/BMJ.galenos.2021.2021.10-17

Research

Digit Ratio (Ratio of Second and Fourth Digit Lengths) in Turkish Male Patients with Myocardial Infarction

Miyokard Enfarktüsü Geçiren Türk Erkek Hastalarda İkinci ve Dördüncü Parmak Oranının Değerlendirilmesi

Fatma Nihan Turhan Çağlar, Cennet Yıldız, Ece Çelebi Coşkun

University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, Istanbul, Turkey

ABSTRACT

Objective: Digit ratio (ratio of second and fourth digit lengths or 2D:4D) is assumed to be negatively correlated with prenatal testosterone level. Prenatal hormonal exposure is associated with various diseases in adulthood; however, data regarding the relationship between 2D:4D ratios and myocardial infarction (MI) localization and demographic characteristics of male patients with a history of MI is limited. Thus, this study aimed to evaluate the association between 2D:4D ratios and history of MI in male patients in respect to cardiovascular risk factors and MI localization.

Methods: The ratios of 2D:4D of both hands of 140 consecutive male patients with a history of MI were measured and recorded. The right and left-hand 2D:4D ratios were compared among different age groups, cardiovascular risk factors, and MI localization.

Results: The average age of participants was 57.56±11.27 years, 13.6% (n=19) of cases were 30-45, 32.1% (n=45) were 46-55, 28.6% (n=40) were 56-65, and 25.7% (n=36) were over 65 years old. Average digit ratio of the right and left hand were 0.98±0.05 cm and 0.96±0.04 cm, respectively. The right versus left 2D:4D was not statistically different according to any age groups, cardiovascular risk factors, and MI localization (p>0.05).

Conclusion: No differences were found in 2D:4D digit ratios of both hands in Turkish male patients with MI history and were not associated with cardiovascular risk factors and MI localization.

Keywords: Myocardial infarction, digit ratio (2D:4D), testosterone

ÖZ

Amaç: İkinci parmak ve 4. parmak (2D:4D) oranının doğum öncesi testesteron seviyesi ile negatif ilişki gösterdiği düşünülmektedir. Doğum öncesi hormon seviyelerinin yetişkinlikte pek çok hastalık ile birlikte olmasına rağmen, 2D:4D oranı ile miyokardiyal enfartüs (MI) lokalizasyonu ve MI anamnezi olan erkek hastaların demografik özellikleri hakkındaki veriler sınırlıdır. Bu çalışmada MI anamnezi olan erkek hastalarda 2D:4D oranı ile kardiyovasküler risk faktörleri ile MI lokalizasyonu arasındaki olası ilişkileri değerlendirmeyi amaçladık.

Gereç ve Yöntem: MI anamnezi olan ardışık 140 erkek hastanın 2D:4D oranı ölçüldü. Sağ ve sol el 2D:4D oranı kardiyovasküler risk faktörleri, MI lokalizasyonu ve yaş grupları açısından değerlendirildi.

Bulgular: Ortalama yaş 57,56±11,27 yıl idi. Hastaların %13,6 (n=19) yaşı 30-45 yıl, %32,1 (n=45) yaşı 46-55 yıl, %28,6 (n=40) yaşı 56-65 yıl ve %25,7 (n=36) 65 yaş üstü idi. Sağ el ve sol el 2D:4D ölçümleri sırası ile 0,98±0,05 ve 0,96±0,04 cm olarak saptandı (p>0,05). Her iki el 2D:4D oranı yaş gruplarına, koroner arter hastalığı risk faktörlerine ve MI lokalizasyonuna göre farklılık göstermedi.

Sonuç: MI geçirmiş olan Türk erkek hastalarda her sağ-sol el 2D:4D oranı, kardiyovasküler risk faktörleri ve MI lokalizasyonu açısından fark gözlenmemiştir.

Anahtar Kelimeler: Miyokard enfartküsü, parmak oranı (2D:4D), testosteron

Address for Correspondence: Fatma Nihan Turhan Çağlar, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, Istanbul, Turkey
Phone: +90 532 687 91 01 E-mail: nhnturhan@gmail.com ORCID ID: orcid.org/0000-0001-7925-2398

Cite as: Turhan Çağlar FN, Yıldız C, Çelebi Coşkun E. Digit Ratio (Ratio of Second and Fourth Digit Lengths) in Turkish Male Patients with Myocardial Infarction. Med J Bakirkoy 2021;17:407-411

Received: 1.11.2021
Accepted: 30.11.2021

INTRODUCTION

The human ratio of the second finger (index finger) to the fourth finger (ring finger) length (2D:4D) is smaller in males compared to females (1). Previous studies revealed that fetal testosterone and estrogen exposure may affect this ratio (1,2). Higher 2D:4D is associated with increased intrauterine exposure to luteinizing hormone, prolactin, and estrogen levels, and decreased testosterone exposure (3-5). The fetal testosterone/estrogen ratio in the amniotic fluid was negatively correlated with the 2D:4D ratio. Moreover, patients with Klinefelter's syndrome had a higher 2D:4D ratio compared to their normal counterparts (1-3) The 2D:4D ratio in humans also varies between ethnic groups, for example, Afro-Caribbean Jamaicans had a lower ratio compared to Caucasian Uygurs (4). Its relationship with various physiological, behavioral, and pathological conditions, such as obesity and metabolic syndrome, has been demonstrated in various studies (5-9). Patients with female congenital adrenal hyperplasia had a higher 2D:4D ratio compared to controls (6).

Traditional coronary artery disease (CAD) risk factors are clearly-defined, whereas the effect of different risk factors, such as genetic predisposition and inflammatory markers, are still evaluated (10). Myocardial infarction (MI) prevalence is higher in males than females in the pre-menopausal period; however, the difference decreases at later ages (11). Additionally, low endogenous testosterone levels are related to MI in males (12). Moreover, a high 2D:4D ratio might be a predisposing factor for MI history at an early age in males (7,8,13). Ozdogmus et al. (9) conducted a study on the autopsy of 100 male patients and revealed that the right-hand ratio was related to atherosclerotic plaque burden in the right coronary arteries.

A small number of studies evaluated the association between 2D:4D and CAD; however, the link between this ratio and age or MI localization has not yet been reported in the literature. Thus, this study aimed to compare 2D:4D ratios according to age, other CAD risk factors, and MI localization in Turkish male patients with MI history.

METHODS

This cross-sectional, single-center, and retrospective study included 140 male patients with previous MI. All patients were from the Turkish ethnic group. Data regarding the demographic characteristics of patients were obtained from hospital registries. Age, presence of diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), history and quantity of smoking, MI localization, and family history were recorded. Acute MI was defined by the criteria of the related guidelines (14). HT was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg at presentation, previous diagnosis of HT, or antihypertensive usage. DM was described as a fasting blood glucose level of ≥126 mg/dL or antidiabetic medication usage. The use of antilipemic agents or serum low-density lipoproteins-cholesterol concentration of >70 mg/dL was described as HL. Patients with hand deformities, thyroid dysfunction, hormonal disorders, genetic diseases, using hormonal therapies, and left-hand users were excluded. Our Hospital Local Ethics Committee University of Health Sciences Istanbul, Turkey Bakırköy Dr. Sadi Konuk Training and Research Hospital approved the study and informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki (ethical approval number: 2018-12-04, date: 06. 25.2018).

Measurement of Finger Lengths

The index and ring finger lengths of both hands were measured using a ruler in the palmar surface, starting from the proximal palm's basal crease to the tip of the finger. An independent examiner blinded to the study measured the finger lengths and calculated the 2D:4D ratio.

Statistical Analysis

Data were statistically analyzed using the Number Cruncher Statistical System 2007 (Kaysville, Utah, USA). Data were expressed as mean, standard deviation, median, frequency, percentage, minimum, and maximum. Normal distribution conformity of quantitative data has been tested with the Shapiro-Wilk test and graphical examinations. Comparison of quantitative variables of two groups with normal distribution was made by the Student's t-test. One-Way analysis of variance and Kruskal-Wallis test was used for the comparison of parametric and non-parametric variables of more than two groups, respectively.

RESULTS

The group average age was 57.56±11.27 years, wherein 13.6% (n=19) of patients were aged 30-45, 32.1% (n=45) were 46-55, 28.6% (n=40) were 56-65 years, and 25.7% (n=36) were over 65 years. Inferior MI was determined in 48.6% (n=68) of patients, anterior MI in 32.9% (n=46), septal MI in 3.6% (n=5), posterior MI in 2.9% (n=4), and lateral MI in 12.1% (n=17). Table 1 shows the demographic characteristics of the study population. Finger length measurements of the total group are summarized in Table 2. The average right-

Table 1. Demographic characteristics of patients

	Total	57.56±11.27
Age n (%)	30-45 years	19 (13.6)
	46-55 years	45 (32.1)
	56-65 years	40 (28.6)
	>65 years	36 (25.7)
Diabetes, n (%)	-	35 (25.0)
Hypertension, n (%)	-	53 (37.9)
Smoking, n (%)	-	118 (84.3)
Family history, n (%)	-	31 (22.1)
Hyperlipidemia	-	33(23.5)
MI localization, n (%)	Inferior MI	68 (48.6)
	Anterior MI	46 (32.9)
	Septal MI	5 (3.6)
	Posterior MI	4 (2.9)
	Lateral MI	17 (12.1)

MI: Myocardial infarction

Table 2. Finger length measurements of patients

	Mean ± SD
Right 2nd finger (mm)	72.93±5.80
Right 4th finger (mm)	74.24±6.89
Right 2nd/ 4th finger	0.98±0.05
Left 2nd finger (mm)	71.55±6.91
Left 4th finger (mm)	74.49±6.50
Left 2nd / 4th finger	0.96±0.04

SD: Standard deviation

hand finger ratio was 0.98±0.05 cm and left hand was 0.96±0.04 cm. Table 3 demonstrates the comparison of left-right 2D:4D according to age subgroups, CAD risk factors, and MI localization. The right versus left 2D:4D was not statistically different according to any age groups, CAD risk factors, or MI localization (p>0.05).

DISCUSSION

This study revealed no statistically significant differences in the 2D:4D ratio of both hands according to age groups, presence of DM, HT, smoking, family history, or MI localization. To the best of our knowledge, the present study was the first one that evaluates the association between the 2D:4D ratio and MI in different age groups, CAD risk factors, and MI localization.

Table 3. Right and left-hand 2D:4D ratio according to age, cardiovascular risk factors, and MI localization

Mean ± SD		Right	Left
		Mean ± SD	
Age	30-45 years (n=19)	0.99±0.04	0.95±0.05
	46-55 years (n=45)	0.98±0.04	0.96±0.05
	56-65 years (n=40)	0.97±0.06	0.95±0.04
	>65 years (n=36)	0.98±0.05	0.96±0.04
	p	[a]0.580	[a]0.432
Diabetes	-	0.98±0.05	0.95±0.05
	p	[b]0.765	[b]0.573
Hypertension	-	0.97±0.05	0.95±0.04
	p	[b]0.109	[b]0.754
Hyperlipidemia	-	0.98±0.05	0.95±0.05
	p	[b]0.741	[b]0.774
Smoking	-	0.98±0.05	0.96±0.04
	p	[b]0.534	[b]0.483
Family History	-	0.98±0.05	0.95±0.04
	p	[b]0.741	[b]0.773
MI localization	Inferior (n=68)	0.98±0.05	0.96±0.05
	Anterior (n=46)	0.98±0.04	0.96±0.04
	Septal (n=5)	0.98±0.05	0.96±0.02
	Posterior (n=4)	0.95±0.03	0.91±0.04
	Lateral (n=17)	0.99±0.05	0.96±0.03
	p	[c]0.686	[c]0.397

[a]One-Way ANOVA, [b]Student's t-test, [c]Kruskal-Wallis test, MI: Myocardial infarction, SD: Standard deviation

Prenatal exposure to androgenic hormones has been shown to affect the digit ratio of humans. Malas et al. (15) revealed that female fetuses have higher 2D:4D digit ratios than males. A study conducted by Lutchmaya et al. (1) revealed that 2D:4D ratios of 2-year-old children were associated with high fetal testosterone levels in the amniotic fluid with estradiol. Additionally, the right hand was more sensitive to the effect of sex steroids than the left. Other studies also showed that testosterone exposure is more effective in the development of the right side of the body than the left side (16,17). The 2D:4D ratio of the right hand and waist-body circumference, which is a predictor for metabolic syndrome, was demonstrated to be statistically significantly higher than the left hand (5). Although statistically insignificant, the

2D:4D ratio of the right hand was also higher than the left hand in our study.

The changes of the 2D:4D after birth are controversial. Studies on this topic have found conflicting findings. Some research found lower 2D:4D ratios in the prenatal period compared to childhood and adulthood, which indicates that the digit ratio increases after birth (18). A longitudinal study reported that an increased 2D:4D was less marked in the right hand, which is more likely to be affected by prenatal steroid levels (19). Contrarily, some data indicate relatively stable values of 2D:4D ratios during lifetime (20). Similarly, our study revealed that the right and left-hand 2D:4D ratios were not different among the age groups.

Previous studies revealed that the 2D:4D ratio was a predictor of CAD (7,8,21,22). Chinese females with CAD had a lower 2D:4D ratio compared to control subjects (23). Viveka et al. (24) revealed a strong association between finger ratio and diagonal ear lobe crease, which is also considered as an indicator of atherosclerosis. Ozdogmus et al. (9) demonstrated that males who had atherosclerotic plaque in the right coronary arteries had a higher right-hand 2D:4D ratio than males without plaques. Wu et al. (21) revealed a higher 2D:4D ratio in males with CAD than females with CAD, as well as a positive correlation between the 2D:4D ratio and CAD in males, but not in females. Additionally, the right-hand 2D:4D ratio had higher discriminative power for CAD. Another study showed that males with a high right-hand digit ratio had MI at a younger age compared to subjects with a low digit ratio (13). The right side of the body is more androgen-sensitive during the prenatal period and the low right-hand digit ratio is correlated with high prenatal and adult testosterone levels. High testosterone levels are is known to be protective against CAD and MI in males. The right and left sides of the body react differently to androgenic stimulation, thus an association between MI localization with the right and left-hand 2D:4D ratios was investigated. Our study revealed that MI localization was not different between the right and left-hand measurements. Similarly, the 2D:4D ratio has been linked to CAD risk factors, including HT, DM, and metabolic syndrome (5,25). Our results revealed that the right and left-hand digit ratios were not different in our study group in their CAD risk factors.

Study Limitations

The present study was a single-center study with a relatively small sample size, which may limit the generalization of our results. Only the 2D:4D ratio in male patients with MI history was measured without a control group that included subjects without MI history. However, studies are reported in the literature, which compared the 2D:4D ratio in MI versus healthy patients (19). Hence, our study aimed to evaluate the 2D:4D ratio in different age subgroups, CAD risk factors, and MI localization to add new findings to the current literature.

CONCLUSIONS

In male patients with MI history, the 2D:4D ratio is not associated with CAD risk factors and MI localization.

ETHICS

Ethics Committee Approval: Our Hospital Local Ethics Committee University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital approved the study. The study was conducted in accordance with the principles of the Declaration of Helsinki (ethical approval number: 2018-12-04, date: 06. 25.2018).

Informed Consent: Informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: E.Ç.C., Concept: F.N.T.Ç., Design: F.N.T.Ç., E.Ç.C., Data Collection or Processing: E.Ç.C., Analysis or Interpretation: C.Y., Literature Search: C.Y., Writing: F.N.T.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. Lutchmaya S, Baron-Cohen S, Raggatt P, Knickmeyer R, Manning JT. 2nd to 4th digit ratios, fetal testosterone and estradiol. Early Hum Dev 2004;77:23-8.
2. Knickmeyer RC, Woolson S, Hamer RM, Konneker T, Gilmore J. 2D:4D ratios in the first 2 years of life: stability and relation to testosterone exposure and sensitivity. Horm Behav 2011;60:256-63.
3. Manning JT, Kilduff LP, Trivers R. Digit ratio (2D: 4D) in Klinefelter's syndrome. Andrology 2013;1:94-9.
4. Manning JT, Stewart A, Bundred PE, Trivers RL. Sex and ethnic differences in 2nd to 4th digit ratio of children. Early Hum Dev 2004;80:161-8.
5. Oyeyemi BF, Iyiola OA, Oyeyemi AW, Oricha KA, Anifowoshe AT, Alamukii NA. Sexual dimorphism in ratio of second and fourth digits and its relationship with metabolic syndrome indices and cardiovascular risk factors. J Res Med Sci 2014;19:234-9.
6. Okten A, Kalyoncu M, Yariş N. The ratio of second- and fourth-digit lengths and congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Early Hum Dev 2002;70:47-54.
7. Manning JT, Bundred PE, Kasielska-Trojanc A, Smith-Straneyd T, Mason L. Digit ratio (2D:4D), myocardial infarction and fibrinogen in men. Early Hum Dev 2019;133:18-22.
8. Fink B, Manning JT, Neave N. The 2nd-4th digit ratio (2D:4D) and neck circumference: implications for risk factors in coronary heart disease. Int J Obes (Lond) 2006;30:711-4.

9. Ozdogmus O, Çakmak YO, Coskun M, Verimli U, Cavdar S, Uzun I. The high 2D:4D finger length ratio effects on atherosclerotic plaque development. Atherosclerosis 2010;209:195-6.
10. Caglar FNT, Biyik İ, Isıksacan N, Hancer VS, Akturk IF, Ciftci S, et al. P-selectin glycoprotein ligand-1 variable number of tandem repeats polymorphism in young myocardial infarction patients. Arc Med Sci Civil Dis 2016;1:112-6.
11. Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. World Health Stat Q 1988;41:155-78.
12. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821-5.
13. Manning JT, Bundred PE. The ratio of 2nd to 4th digit length and age at first myocardial infarction in men: a link with testosterone? Br J Cardiol 2001;8:720-3.
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Glob Heart 2018;13:305-38.
15. Malas MA, Dogan S, Evcil EH, Desdicioglu K. Fetal development of the hand, digits and digit ratio (2D:4D). Early Hum Dev 2006;82:469-75.
16. Kraemer B, Noll T, Delsignore A, Milos G, Schnyder U, Hepp U. Finger length ratio (2D:4D) and dimensions of sexual orientation. Neuropsychobiology 2006;53:210-4.
17. Hönekopp J, Watson S. Meta-analysis of digit ratio 2D:4D shows greater sex difference in the right hand. Am J Hum Biol 2010;22:619-30.
18. Galis F, Ten Broek CM, Van Dongen S, Wijnaendts LC. Sexual dimorphism in the prenatal digit ratio (2D:4D). Arch Sex Behav 2010;39:57-62.
19. Trivers R, Manning J, Jacobson A. A longitudinal study of digit ratio (2D:4D) and other finger ratios in Jamaican children. Horm Behav 2006;49:150-6.
20. Manning JT, Scutt D, J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 1998;13:3000-4.
21. Wu XL, Yang DY, Chai WH, Jin ML, Zhou XC, Peng L, et al. The ratio of second to fourth digit length (2D:4D) and coronary artery disease in a Han Chinese population. Int J Med Sci 2013;10:1584-8.
22. Kyriakidis I, Papaioannidou P, Pantelidou V, Kalles V, Gemitzis K. Digit ratios and relation to myocardial infarction in Greek men and women. Gend Med 2010;7:628-36.
23. Wang L, Huo Z, Lu H, Bai C, Li C, Ma. Digit ratio (2D:4D) and coronary artery disease in north Chinese women. Early Hum Dev 2018;116:64-7.
24. Viveka S, Sagar TV, Kumar JA. Evaluation of 2D:4D digit ratio and diagonal earlobe crease as markersof coronary artery disease. Journal of the Anatomical Society of India 2016;65:148-51.
25. Asuku A, Danborno B, Akuyam S, Timbuak J, Mohammed A, Adamu L. Reference values of body adiposity measures and hand digit ratio (2D:4D) for dyslipidemia: A case study of the Hausa ethnic group in Kano, Nigeria. Journal of Experimental and Clinical Anatomy 2019;18:30

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:412-419
DOI: 10.4274/BMJ.galenos.2021.2021.10-9

Research

The Comparison of Intraoperative Pressure Control and Volume Control Ventilation in Supine and Prone Positions: The Endless Debate

İntraoperatif Mekanik Ventilasyonda Supine ve Prone Pozisyonlarda Basınç Kontrol ile Volüm Kontrol Modlarının Karşılaştırılması: Bitmeyen Tartışma, PCV mi? VCV mi?

Sinan Aşar[1], Furkan Tontu[2], Gülay Aşık Eren[3]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
[2]Ağrı Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ağrı, Turkey
[3]Near East University Hospital, Clinic of Anesthesiology and Reanimation, Nicosia, TRNC

ABSTRACT

Objective: Position (supine and prone) changes have their essential effects on respiratory mechanics and pulmonary perfusion in patients under general anesthesia. These effects on respiratory mechanics, arterial blood gas, and hemodynamic parameters in patients who underwent percutaneous nephrolithotomy operation were compared in pressure and volume control ventilation (VCV) modes.

Methods: This study prospectively evaluated 50 patients who underwent percutaneous nephrolithotomy. Patients were divided into groups of VCV and pressure control ventilation (PCV). Each group was divided further into two subgroups with supine and prone positions. General anesthesia was applied to all patients. Respiratory mechanics were recorded every 5 min. Arterial blood gas samples were repeated at each position change. Hemodynamic and respiratory parameters were simultaneously recorded.

Results: Peak inspiratory pressure (Ppeak), plateau pressure (Pplato), and driving pressure (DP) of the VCV group were higher in the prone position than in the supine position. Ppeak, Pplato, and DP in the prone position were higher in the VCV group than the PCV group, and Horowitz ratio and compliance were lower. The Horowitz ratio of both groups was significantly higher in the prone than in the supine position.

Conclusion: Despite the advantages, the superiority of PCV to VCV cannot be mentioned at the present.

Keywords: Volume control, pressure control, prone, supine, driving pressure

ÖZ

Amaç: Anestezi altındaki hastalarda pozisyon değişikliklerinin solunum mekanikleri ve pulmoner perfüzyon üzerine önemli etkileri mevcuttur. Perkütan nefrolitotomi operasyonu yapılan hastalara verilen pozisyonların (supine ve prone) solunum mekanikleri, arter kan gazı ve hemodinamik parametreler üzerine olan etkileri basınç kontrol ve volüm kontrol modlarında karşılaştırılmıştır.

Gereç ve Yöntem: Perkütan nefrolitotomi operasyonu planlanan 50 hasta prospektif olarak değerlendirildi. Hastalar volüm kontrol ve basınç kontrol grupları olarak ikiye ayrıldı. Her grup supine ve prone pozisyonları olacak şekilde iki subgruba ayrıldı. Tüm hastalara genel anestezi uygulandı. Solunum mekanikleri 5 dakika ara ile kaydedildi. Arter kan gazı örnekleri her pozisyon değişiminde tekrarlandı. Hemodinamik parametreler ve solunum parametreleri eş zamanlı olarak kaydedildi. Hasta ortalamaları alındıktan sonra gruplar Student's t-testi, grup içi parametreler ise Paired t-testi ile karşılaştırıldı.

Bulgular: Volüm kontrol grubunda prone pozisyonunda peak insipiratuar basıncı (Ppeak), plato basıncı (Pplato) ve sürücü basıncı (Driving Pressure: DP) supine pozisyonundaki değerlerden daha yüksek bulunmuştur. Her iki grubun prone pozisyon Horowitz oranı, supine pozisyon değerlerinden anlamlı derecede yüksek bulunmuştur. Prone pozisyonda, volüm kontrol grubunun basınç kontrol grubuna göre Ppeak, Pplato ve DP değerleri daha yüksek; kompliyans ve Horowitz oranı ise daha düşük hesaplanmıştır.

Address for Correspondence: Sinan Aşar, University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
Phone: +90 544 265 98 44 E-mail: sinan.asaras@gmail.com ORCID ID: orcid.org/0000-0001-5787-5885

Cite as: Aşar S, Tontu F, Aşık Eren G. The Comparison of Intraoperative Pressure Control and Volume Control Ventilation in Supine and Prone Positions: The Endless Debate. Med J Bakirkoy 2021;17:412-419

Received: 04.11.2021
Accepted: 30.11.2021

Sonuç: Horowitz oranı, hem volüm kontrol hem de basınç kontrol ventilasyonda, prone pozisyonda supine pozisyondan yüksek bulunmuştur. Basınç kontrol grubunda, volüm kontrol grubuna göre; daha düşük DP, daha yüksek akciğer kompliyansı ve daha yüksek Horowitz oranları hesaplanmıştır. Basınç kontrol modunun avantajlarına rağmen, günümüzde basınç kontrol ile volum kontrol modlarının birbirlerine olan üstünlüğünden bahsetmek söz konusu değildir.

Anahtar Kelimeler: Volüm kontrol, basınç kontrol, prone, supine, sürücü basınç

INTRODUCTION

Percutaneous nephrolithotomy is an invasive surgery that is performed in the supine and prone positions under general anesthesia (1). Depending on the surgical position, various changes occur in all body systems. As preferred by the surgical team, a position that will facilitate the surgical approach but will not endanger cardiovascular and pulmonary functions should be applied (2). Position changes have essential effects on respiratory mechanics and pulmonary perfusion in patients under general anesthesia (3). A 10% and 12.5% decreased vital capacity in the prone and supine positions were found, respectively (2).

Healthy people have decreased lung compliance during the prone position due to thoracal expansion restriction, decreased chest wall elasticity, obesity, neuromuscular blockers, and abdominal compression (4). However, prone positioning, which is also used to improve oxygenation in patients with acute respiratory distress syndrome (ARDS) in the intensive care unit, is a safe and most effective lung-protective ventilation strategy component that includes low positive end-expiratory pressure (PEEP), low tidal volume (TV), and low driving pressure (DP) (5).

Pulmonary blood flow and gas distribution differ according to the supine position in patients who are mechanically ventilated in the prone position (6). Thoracic wall movement is limited by compression. With decreased muscle tone due to neuromuscular blockers, the diaphragm is directed toward the cephalus by intra-abdominal pressure. The resulting changes in the lung volume and pulmonary blood flow differentiation affect the respiratory mechanics (7,8).

Respiratory system compliance decreases by 17-30% when paralyzed patients under general anesthesia are turned to the prone position (9). However, some studies revealed no significant changes in the compliance when the appropriate position (with chest wall and pelvic supports) was given (10,11). A significantly increased functional residual capacity is seen in the prone position, which can be explained by dependent alveoli reopening that tends to close in the supine position (12).

Better oxygenation in the prone position compared to the supine position is achieved by improving the ventilation-perfusion ratio and eliminating lung compression by the heart. Thus, an increased ventilable lung is obtained (13).

Close monitoring of respiratory mechanics is vital in the operating room and the intensive care unit (14). Mechanical ventilation is life-saving; however, it causes ventilator-induced lung injury (VILI) (15). Respiratory parameters, such as TV, DP, flow, respiratory rate, and PEEP, were associated with VILI (16). However, DP was considered the main mediator to cause VILI. Additionally, intraoperative high DP is associated with increased postoperative pulmonary complications (17).

This study compared the respiratory mechanics and blood gas parameters of patients who underwent percutaneous nephrolithotomy and were ventilated with volume control ventilation (VCV) or pressure control ventilation (PCV) in supine and prone positions.

METHODS

Study Population

This study was prospectively conducted in 50 patients who underwent percutaneous nephrolithotomy. Patients with the American Society of Anesthesiologists classification I-II, between the age of 18 and 65 years, without chronic obstructive pulmonary disease, diabetes, and cardiopulmonary diseases was included in the study. All patients underwent preoperative anesthetic evaluation.

Study Design

Patients were sequentially randomized into two groups, first from the VCV group and then from the PCV group. Vascular access was provided to patients after electrocardiogram, noninvasive blood pressure, and oxygen saturation (SpO_2) monitoring. At a rate of 2-4 mL/kg/h, 0.9% NaCl infusion was started. Initial heart rate (HR), mean arterial pressure (MAP), and peripheral SpO_2 were recorded as baseline values. Intravenously, propofol of 2 mg/kg, fentanyl of 2 µg/kg for induction, and vecuronium of 0.1 mg/kg for neuromuscular blockage were given. After endotracheal intubation with a 7.5 mm inner diameter spiral tube, radial artery cannulation was performed. Balanced general anesthesia with sevoflurane of 1 MAC and remifentanil was maintained. The VCV (n=25) and PCV group (n=25) were ventilated with Dräger Primus anesthetic machine (Lübeck, Germany). Ventilation parameters were constant with a respiratory rate of 12/min, PEEP of 5 cm H_2O, and inspiration-expiration rate of 1:2. These settings remained since the end-tidal carbon

dioxide ($EtCO_2$) was in the range of 30-35 in all patients. At the beginning of the operation, all patients were ventilated with a TV of 6-8 mL/kg, and the DP is adjusted to provide this TV in the PCV group. Respiratory and hemodynamic parameters of all patients were recorded at 0, 5, 10,15, 20, 25, and 30 min with 5-min intervals in the supine period after induction. Similarly, 5 min after the patient was turned to the prone position, the data were recorded at 5, 10,15, 20, 25t, 30, and 35 min with 5-min intervals. Arterial blood gas samples were taken at the 30th min in the supine position and the 35th min in the prone position.

Thoracal gel supports were placed on both sides of the chest during prone positioning. After the patients were turned to the supine position at the end of the surgery, inhalation agents were stopped. Atropine of 0.01 mg/kg and neostigmine of 0.03 mg/kg were administered to eliminate residual neuromuscular blockade after spontaneous breathing started. Patients were extubated when spontaneous breathing was sufficient. All patients were hemodynamically stable, without complications.

Compliance, peak inspiratory pressure (Ppeak), plateau pressure (Pplato), DP, $ETCO_2$, HR, MAP, pH, partial arterial carbon dioxide pressure ($PaCO_2$), bicarbonate (HCO_3), and partial arterial oxygen pressure (PaO_2) parameters were recorded as excel file.

The mean values of all data in supine and prone positions were recorded for statistical analyses.

Calculation of DP and Compliance

The gas flow is constant in VCV and 5% pause time (Tpause) is set at the end of inspiration, thus Pplato and compliance are automatically calculated by the ventilator and screen display. In PCV, the airway pressure is considered constant from the beginning to the end of inspiration. Therefore, Ppeak and alveolar pressure (Pplato) are calculated as equal (18-20).

The presence of auto-PEEP was evaluated with the expiratory hold maneuver. However, auto-PEEP was not detected in our patients (Auto - PEEP = PEEPtotal - PEEPset). Since no auto-PEEP exists, DP is calculated as (DP) = Ppeak - PEEP, and compliance is calculated as (C) = Tve ÷ (Ppeak - PEEP) in PCV.

Sample Size Calculation

A pilot study was conducted with five patients to determine the number of patients to be included in the study. The comparison of VCV and PCV in the prone position determined the DP difference as the primary outcome. In the prone position, DP was calculated as 13±2 cmH_2O in VCV and 11±2 cmH_2O in PCV. The sample size was calculated as at least 23 patients per group based on a pilot study (power=95%; α=0.05) (G*Power version 3.1.9.4, Germany).

Statistical Analyses

The gender distribution of the groups was compared using the Chi-square test. Demographic data (age, height, and weight), arterial blood gas, and respiratory parameters of the groups were homogeneous in the Shapiro-Wilk test and were evaluated with the Student's t-test. Subgroup comparisons were made with the paired t-test. The mean and standard deviation (SD) values for each parameter were used for statistical representation. Results were evaluated at the significance level of $p<0.05$. Statistical analyzes were made with Number Cruncher Statistical System 2007 Statistical Software (Utah, USA).

RESULTS

No statistical difference was found between gender distribution and mean ± SD values of age, height, predictive bodyweight of the VCV and PCV groups (Table 1).

A statistically significant difference was observed between the mean values of Ppeak, TV, PaO_2/FiO_2 in the supine position of the VCV and PCV groups, whereas no statistically significant difference between the mean values of Pplato, TV, DP, compliance, $ETCO_2$, $PaCO_2$, HCO_3, pH, HR, and MAP.

A statistically significant difference was observed between the mean values of Ppeak, Pplato, DP, TV, compliance, PaO_2/FiO_2 in the prone position of the VCV and PCV groups, whereas no statistically significant difference between the mean values of $ETCO_2$, $PaCO_2$, HCO_3, pH, HR, and MAP.

The mean ± SD of the above-mentioned respiratory parameters of the VCV and PCV groups in the supine and prone positions are shown in Table 2.

In the VCV group, Ppeak, Pplato, DP, PaO_2, and PaO_2/FiO_2 values were statistically significantly higher, and compliance values were significantly lower in the prone position than the supine position. However, no statistically significant difference was observed between $ETCO_2$, $PaCO_2$, HCO_3, and pH values.

Table 1. Gender distribution between the two groups was compared with the chi-square test. The mean values of age, height, and predictive body weight (PBW) of the two groups were compared by Student's t-test

	VCV group	PCV group	p
Female (%)	11 (11.44%)	9 (9.36%)	**0.24**
Age, years (mean ± SD)	44.2±14.32	39.84±13.56	**0.24**
Height, cm (mean ± SD)	173.086.52	172.045.22	**0.5**
PBW, kg (mean ± SD)	76.52±12.53	71.52±7.07	**0.9**

PBW: Predictive body weight, VCV: Volume control ventilation PCV: Pressure control ventilation SD: Standard deviation

The mean ± SD values of the respiratory parameters in the supine and prone positions of the VCV group are shown in Table 3.

In the PCV group, PaO_2, PaO_2/FiO_2 values were statistically significantly higher, and TV and compliance values were significantly lower in the prone position than the supine position. However, no statistically significant difference was observed between Ppeak, Pplato, and DP values.

The mean ± SD values of respiratory parameters in the supine and prone positions of the PCV group are shown in Table 4.

DISCUSSION

PCV and VCV have been compared for a long time (21-24). Our study re-discussed this issue with current topics, such as DP, under the guidance of previous studies.

The mean PaO_2 values of the PCV group were higher than the VCV group in supine and prone positions. Studies show that PCV provides better PaO_2 values in supine and prone positions than VCV mode (24-29).

No significant difference was found between the $PaCO_2$ values between the PCV and VCV groups in supine and prone positions. Additionally, a recent meta-analysis reported no difference in $PaCO_2$ values between the VCV and PCV groups in patients who had elective surgery in the supine position (24).

In VCV and PCV groups, mean PaO_2 values were statistically significantly lower in the supine than in the prone position. In the prone position, significantly increased PaO_2 values have been attributed to the reduced dependent lung areas and the lesser gravitational effect of the heart and great vessels on the lung (25,26,30,31). Thus, a better perfusion/ventilation ratio is obtained (32). Additionally, increased functional residual capacity and secretion mobilization also contribute to this improvement (26). Many studies have indicated that the prone position positively affects the arterial blood gas parameters (33-35). Our study revealed no difference between the PCO_2 values in position changes in both ventilation modes. Previous studies have shown that $PaCO_2$ values in the prone position are equal or lower than in the supine position (33-35).

Table 2. The comparison of patients in the VCV and PCV groups with the Student's t-test for arterial blood gas results, hemodynamic, and respiratory parameters in the supine and prone positions

VCV (n=25) vs. PCV (n=25)	VCV supine vs. PCV supine	p	VCV prone vs. PCV prone	p
-	mean ± SD vs. mean ± SD	-	mean ± SD vs. mean ± SD	-
Pplato, cm H_2O	15.3±1.9 vs. 15.9±1.1	>0.05	19.3±1.9 vs. 15.9±1.1	**0.0001**
Ppeak, cm H_2O	17.2±1.7 vs. 15.9±1.1	**0.01**	21.7±1.9 vs. 15.9±1.4	**0.001**
DP, cm H_2O	10.1±1.8 vs. 10.9±1.0	>0.05	13.3±1.8 vs. 10.5±1.1	**0.0001**
PEEP, cm H_2O	4.7±0.1 vs. 4.9±0.1	>0.05	4.8±0.1 vs. 4.9±0.1	>0.05
TVe, mL	598±50 vs. 605±60	>0.05	570±40 vs. 516±62	**0.001**
RR, per minute	12 vs. 12	>0.05	12 vs. 12	>0.05
C, mL/cm H_2O	60.6±8.2 vs. 61.2±6.9	>0.05	40.0±6.2 vs. 46.0±5.6	**0.001**
$ETCO_2$, meq/L	30±5 vs. 29±2	>0.05	28±5 vs. 28±2	>0.05
pH	7.45±0.05 vs. 7.44±0.05	>0.05	7.46±0.06 vs. 7.42±0.04	>0.05
HCO_3, meq/L	25±2.1 vs. 24.1±2.2	>0.05	23.4±2.1 vs. 23.1±2.7	>0.05
PCO_2, mmHg	35±5 vs. 34±5	>0.05	33±6 vs. 34±5)	>0.05
PaO_2, mmHg	223±53 vs. 281±66	**0.001**	248±35 vs. 301±53	**0.0001**
FiO_2, %	50 vs. 50	0.05	50 vs. 50	>0.05
PaO_2/FiO_2	446±106 vs. 562±132	**0.001**	496±70 vs. 602±108	**0.0001**
HR, per minute	75±9 vs. 76±7	>0.05	62±6 vs. 63±8	>0.05
MAP, mmHg	81±5 vs. 83±7	>0.05	87±7 vs. 93±9	>0.05

C: Lung compliance, PEEP: Positive end-expiratory pressure, Ppeak: Peak ınspiratory pressure, DP: Driver pressure, TVe: Expiratory tidal volume, Pplato: Plateau pressure, $ETCO_2$: End-tidal carbon dioxide, HR: Heart rate, MAP: Mean arterial pressure, $PaCO_2$: Partial arterial carbon dioxide pressure, PaO_2: Partial arterial oxygen pressure, HCO_3: Bicarbonate, VCV: Volume control ventilation PCV: Pressure control ventilation SD: Standard deviation

Table 3. The comparison of arterial blood gas and respiratory parameters of the VCV group in the supine and prone positions with the paired t-test

VCV group (n=25)	a) Supine position	b) Prone position	p
-	mean ± SD	mean ± SD	-
Pplato, cmH_2O	15±1.9	(19±1.9)	**p<0.0001**
Ppeak, cmH_2O	17.2±1.7	(21.7±1.9)	**p<0.0001**
PEEP, cmH_2O	4.7±0.1	4.8±0.1	p≥0.05
DP, cmH_2O	10.1±1.8	13.3±1.8	**p<0.0001**
Tidal Volume (TV) mL	598±50	570±40	**p<0.01**
RR, 1/min	12	12	p≥0.05
C, mL/cmH_2O	60.6±9.2	(39.9±6.2)	**p<0.0001**
$ETCO_2$, (meq/L)	30±7	30±5	p≥0.05
pH	7.45±0.05	7.46±0.06	p≥0.05
HCO_3, (meq/L)	25±2.0	23±2.1	p≥0.05
PCO_2, (mmHg)	35.±5	34±6	p≥0.05
PaO_2, (mmHg)	223±53	248±35	**p<0.001**
FiO_2, (%)	50	50	p≥0.05
PaO_2/FiO_2	446±106	496±70	**p<0.001**

C: Lung compliance, PEEP: Positive end-expiratory pressure, Ppeak: Peak ınspiratory pressure, DP: Driver pressure, TVe: Expiratory tidal volume, Pplato: Plateau pressure, $ETCO_2$: End-tidal carbon dioxide, HR: Heart rate, MAP: Mean arterial pressure, $PaCO_2$: Partial arterial carbon dioxide pressure, PaO_2: Partial arterial oxygen pressure, HCO_3: Bicarbonate, VCV: Volume control ventilation PCV: Pressure control ventilation SD: Standard deviation

Table 4. Arterial blood gas and respiratory parameters of the PCV group in the supine and prone positions were compared with the paired t-test

PCV group (n=25)	a) Supine position	b) Prone position	p
	mean ± SD	mean ± SD	-
Pplato, cmH_2O	15.9±1.1	15.9±1.1	p≥0.05
Ppeak, cmH_2O	15.9±1.1	15.9±1.1	p≥0.05
PEEP, cmH_2O	4.8±0.1	4.9±0.1	p≥0.05
DP, cmH_2O	10.9±1.0	10.9±1.0	p≥0.05
Tidal Volume (ΔV). mL	630±79	(516±62)	**p<0.0001**
RR, 1/min	12	12	p≥0.05
C, mL/ cmH_2O	64.3±6.9	(46.0±5.6)	**p< 0.0001**
$ETCO_2$, (meq/L)	29±2	(28±2)	p≥0.05
PH	7.44±0.05	7.43±0.04	p≥0.05
HCO_3, (meq/L)	24.1±2.1	23.1±2.7	p≥0.05
PCO_2, (mmHg)	34±5	34±5	33±5
PaO_2, (mmHg)	281±66	(301±53)	p<0.01
FiO_2, (%)	50	50	p≥0.05
PaO_2/FiO_2	562±132	(602±108)	p<0.01

C: Lung compliance, PEEP: Positive end-expiratory pressure, Ppeak: Peak ınspiratory pressure, DP: Driver pressure, TVe: Expiratory tidal volume, Pplato: Plateau pressure, $ETCO_2$: End-tidal carbon dioxide, HR: Heart rate, MAP: Mean arterial pressure, $PaCO_2$: Partial arterial carbon dioxide pressure, PaO_2: Partial arterial oxygen pressure, HCO_3: Bicarbonate, VCV: Volume control ventilation PCV: Pressure control ventilation SD: Standard deviation

At the beginning of the operation, despite higher TV in the PCV group, no significant difference was found between the Pplato values in the supine position of the PCV and VCV groups. However, after the patient was turned to the prone position, the Pplato values of the PCV group were lower than the VCV group, although the other set of respiratory parameters (DP in PCV and TV in VCV) were constant. Similarly, Ppeak values of the PCV group were also lower in both positions. Studies report that Ppeak and Pplato values of the VCV group in the prone position are equal or higher than in the supine position (10,26,36). Another study that ventilated patients with VCV after anesthesia induction and pneumoperitoneum revealed decreased Pplato values when the ventilation mode was changed to PCV after 40 min (35). A meta-analysis reported lower intraoperative Ppeak and Pplato values in PCV (29).

The lower Ppeak and Pplato values in the PCV group were attributed to the different gas flow patterns between the two groups (35). Therefore, no difference was found between the DP values of the VCV and PCV groups in the supine position but a significant difference in the prone position. Similarly, DP values of the VCV group were significantly different between positions. The DP is constant in both positions in PCV, thus homogeneous ventilation of the alveoli with different time constants is ensured and prevented excessive bronchoalveolar unit stretching (26,35-37).

No difference was found between the compliance of the VCV and PCV groups in the supine position. However, when the patients were turned to the prone position without changing their respiratory settings, the compliance was significantly higher in the PCV group than the VCV group. The compliance of the VCV and PCV groups in the supine position was statistically significantly higher than in the prone position. The reduced compliance of the VCV group when patients are turned to the prone position is thought to be due to the increased Ppeak and Pplato. Contrarily, Ppeak and Pplato are constant in PCV, thus the reduced compliance is due to the decreased TV. Reduced lung compliance in the prone position is due to the increased abdominal pressure to the thorax due to neuromuscular blockers, thoracal movement restriction, and chest wall compression by the support materials (26,35,37). The study of Sen et al. (38)

in percutaneous nephrolithotomy patients compared the PCV and VCV modes in the prone and supine positions, and compliance was found to be lower in both modes in the prone position. The compliance of the PCV group in the prone position was found to be higher than the VCV group (38). The compliance decreases from supine to the prone position by approximately 17% to 30% (9). However, studies report that compliance in the prone position will not change with correctly placed thoracal and pelvic supports (10,11). Compliance was observed to significantly increase when switching from VCV to PCV after anesthesia induction (35). In patients who underwent laparoscopic gynecological surgery, lung compliance was higher in PCV than VCV (39). Changes in compliance are due to the gas flow pattern. The decreasing flow pattern in the PCV is argued to reduce lung tension. However, changes in compliance while isovolumetric depend not only on the elastic properties of the respiratory system but also on the resistive component of the airway and endotracheal tube (26,35).

Respiratory dynamic changes in the prone position mentioned above are due to the need for a higher DP to reach the set TV in VCV and the lower TV to reach the set DP in PCV.

High DP was strongly associated with VILI and mortality (40). Additionally, high DP on the first day of mechanical ventilation is a risk factor for ARDS development later on (41) and is also associated with postoperative pulmonary complications (17). Therefore, obtaining a better gas exchange with lower DP gave PCV an advantage over VCV. Compared to the VCV group, the PCV group had lower DP and better gas exchange. However, this advantage of PCV has recently become controversial (42) since reaching inspiratory pressure (DP) in a short time interval (T-slope) with the highly variable gas flow in PCV can have a damaging effect. These theoretical concerns regarding the PCV should be seen as worthy of investigation.

Postoperative pulmonary complications develop in 5%-33% of patients. These complications were shown to reduce with lung-protective ventilation. For lung-protective ventilation in the surgical patient, an international expert panel recommends that Cdyn, DP, and Pplato should be monitored on all mechanically controlled ventilated patients, and currently, a preferred specific ventilation mode is not recommended, as studies are reporting conflicting results (43).

Our study has some limitations. First, airway resistance parameters were not compared between ventilation modes since inspiratory resistance values in PCV were not automatically calculated by the ventilator, and we did not have the opportunity to calculate with the least-square fit method (44). Second, the effects of both ventilation modes and position changes on advanced hemodynamic parameters (central venous pressure, cardiac output, systemic vascular resistance, and lung water) have not been studied. Third, neuromuscular blockade monitoring could not be performed.

CONCLUSION

Prone position was beneficial as it increased oxygenation in both the VCV and PCV groups without causing any adverse effects on hemodynamic and respiratory mechanics. The PCV group had better respiratory mechanics (lower DP and Pplato) and blood gas parameters (higher PaO_2) than the VCV group in the prone position. However, today, the superiority of PCV and VCV over each other cannot be mentioned.

ACKNOWLEDGMENTS

The authors would like to thank Oya Hergünsel for her valuable support.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from University of Healht Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (code: 2009/106, date: 06.18.2009). The research conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Brazil 2013).

Informed Consent: Written consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: S.A., Concept: S.A., G.A.E., Design: S.A., F.T., G.A.E., Data Collection or Processing: S.A., Analysis or Interpretation: S.A., F.T., Literature Search: S.A., F.T., Writing: S.A., F.T., G.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. Miano R, Scoffone C, De Nunzio C, Germani S, Cracco C, Usai P, et al. Position: prone or supine is the issue of percutaneous nephrolithotomy. J Endourol 2010;24:931-8.
2. Richter T, Bellani G, Scott Harris R, Vidal Melo MF, Winkler T, Venegas JG, et al. Effect of prone position on regional shunt, aeration, and perfusion in experimental acute lung injury. Am J Respir Crit Care Med 2005;172:480-7.

3. Tanskanen P, Kyttä J, Randell T. The effect of patient positioning on dynamic lung compliance. Acta Anaesthesiol Scand 1997;41:602-6.
4. Halbertsma F, Van der Hoeven JG. Lung recruitment during mechanical positive pressure ventilation in the PICU: what can be learned from the literature? Anaesthesia 2005;60:779-90.
5. Guérin C, Albert RK, Beitler J, Gattinoni L, Jaber S, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med 2020;46:2385-96.
6. Johannigman JA, Davis K Jr, Miller SL, Campbell RS, Luchette FA, Frame SB, et al. Prone positioning and inhaled nitric oxide: synergistic therapies for acute respiratory distress syndrome. J Trauma Acute Care Surg 2001;50:595-6.
7. Damia G, Mascheroni D, Croci M, Tarenzi L. Perioperative changes in functional residual capacity in morbidly obese patients. Br J Anaesth 988;60:574-8.
8. Pelosi P, Croci M, Calappi E, Mulazzi D, Cerisara M, Vercesi P, et al. Prone positioning improves pulmonary function in obese patients during general anesthesia. Anesth Analg 1996;83:578-83.
9. Soro M, García-Pérez ML, Belda FJ, Ferrandis R, Aguilar G, Tusman G, et al. Effects of prone position on alveolar dead space and gas exchange during general anaesthesia in surgery of long duration. Eur J Anaesthesiol 2007;24:431-7.
10. Pelosi P, Croci M, Calappi E, Cerisara M, Mulazzi D, Vicardi P, et al. The prone positioning during general anesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Anesth Analg 1995;80:955-60.
11. Palmon SC, Kirsch JR, Depper JA, Toung TJ. The effect of the prone position on pulmonary mechanics is frame-dependent. Anesth Analg 1998;87:1175-80.
12. Hedenstierna G, Tokics L, Strandberg Å, Lundquist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. Acta Anaesthesiol Scand 1986;30:183-91.
13. Glenny RW, Lamm W, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. J Appl Physiol 1991;71:620-9.
14. Ball L, Costantino F, Fiorito M, Amodio S, Pelosi P. Respiratory mechanics during general anaesthesia. Ann Transl Med 2018;6:379.
15. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J 2013;369:2126-36.
16. Hotchkiss JR Jr, Blanch L, Murias G, Adams AB, Olson DA, Wangensteen OD, et al. Effects of decreased respiratory frequency on ventilator-induced lung injury. Am J Respir Crit Care Med 2000;161:463-8.
17. Neto AS, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. Lancet Respir Med 2016;4:272-80.
18. van der Meijden S, Molenaar M, Somhorst P, Schoe A. Calculating mechanical power for pressure-controlled ventilation. Intensive Care Med 2019;45:1495-7.
19. Silva PL, Ball L, Rocco PRM, Pelosi P. Power to mechanical power to minimize ventilator-induced lung injury? Intensive Care Med Exp 2019;7(Suppl 1):38.
20. Ashworth L, Norisue Y, Koster M, Anderson J, Takada J, Ebisu H. Clinical management of pressure control ventilation: An algorithmic method of patient ventilatory management to address "forgotten but important variables". J Crit Care 2018;43:169-82.
21. Campbell RS, Davis BR. Pressure-controlled versus volume-controlled ventilation: does it matter? Respir Care 2002;47:416-26.
22. Chacko B, Peter JV, Tharyan P, John G, Jeyaseelan L. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev 2015;1:CD008807.
23. Lee JM, Lee SK, Kim KM, Kim YJ, Park EY. Comparison of volume-controlled ventilation mode and pressure-controlled ventilation with volume-guaranteed mode in the prone position during lumbar spine surgery. BMC Anesthesiol 2019;19:133.
24. Schick V, Dusse F, Eckardt R, Kerkhoff S, Commotio S, Hinkelbein J, et al. Comparison of Volume-Guaranteed or -Targeted, Pressure-Controlled Ventilation with Volume-Controlled Ventilation during Elective Surgery: A Systematic Review and Meta-Analysis. J Clin Med 2021;10:1276.
25. Cakar N, der Kloot TV, Youngblood M, Adams A, Nahum A. Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. Am J Respir Crit Care Med 2000;161:1949-56.
26. Manna EM, Ibraheim OA, Samarkandi AH, Alotaibi WM, Elwatidy SM. The effect of prone position on respiratory mechanics during spinal surgery. Middle East J Anaesthesiol 2005;18:623-30.
27. Lee JM, Lee SK, Rhim CC, Seo KH, Han M, Kim SY, et al. Comparison of volume-controlled, pressure-controlled, and pressure-controlled volume-guaranteed ventilation during robot-assisted laparoscopic gynecologic surgery in the Trendelenburg position. Int J Med Sci 2020;17:2728-34.
28. Kim MS, Soh S, Kim SY, Song MS, Park JH. Comparisons of Pressure-controlled Ventilation with Volume Guarantee and Volume-controlled 1:1 Equal Ratio Ventilation on Oxygenation and Respiratory Mechanics during Robot-assisted Laparoscopic Radical Prostatectomy: a Randomized-controlled Trial. Int J Med Sci 2018;15:1522-9.
29. Jiang J, Li B, Kang N, Wu A, Yue Y. Pressure-Controlled Versus Volume-Controlled Ventilation for Surgical Patients: A Systematic Review and Meta-analysis. J Cardiothorac Vasc Anesth 2016;30:501-14.
30. Mezidi M, Guérin C. Effects of patient positioning on respiratory mechanics in mechanically ventilated ICU patients. Ann Transl Med 2018;6:384.
31. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS With Prone Positioning. Chest 2017;151:215-24.
32. Mure M, Domino KB, Lindahl SG, Hlastala MP, Altemeier WA, Glenny RW. Regional ventilation-perfusion distribution is more uniform in the prone position. J Appl Physiol (1985) 2000;88:1076-83.
33. Magi E, Multari G, Recine C, Barberio O, Becattini G, Tellini A. [Difference between arterial and end-tidal carbon dioxide tension during surgery of lumbar herniated disk in general anesthesia]. Minerva Anestesiol 1994;60:381-6.
34. Wahba RW, Tessler MJ, Kardash KJ. Carbon dioxide tensions during anesthesia in the prone position. Anesth Analg 1998;86:668-9.
35. Balick-Weber CC, Nicolas P, Hedreville-Montout M, Blanchet P, Stéphan F. Respiratory and haemodynamic effects of volume-controlled vs pressure-controlled ventilation during laparoscopy: a cross-over study with echocardiographic assessment. Br J Anaesth 2007;99:429-35.
36. De Baerdemaeker LE, Van der Herten C, Gillardin JM, Pattyn P, Mortier EP, Szegedi LL. Comparison of volume-controlled and pressure-controlled ventilation during laparoscopic gastric banding in morbidly obese patients. Obes Surg 2008;18:680-5.
37. Cox RG, Ewen A, Bart BB. The prone position is associated with a decrease in respiratory system compliance in healthy anaesthetized infants. Paediatr Anaesth 2001;11:291-6.

38. Sen O, Bakan M, Umutoglu T, Aydın N, Toptas M, Akkoc I. Effects of pressure-controlled and volume-controlled ventilation on respiratory mechanics and systemic stress response during prone position. Springerplus 2016;5:1761.
39. Oğurlu M, Küçük M, Bilgin F, Sizlan A, Yanarateş O, Eksert S, et al. Pressure-controlled vs volume-controlled ventilation during laparoscopic gynecologic surgery. J Minim Invasive Gynecol 2010;17:295-300.
40. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372:747-55.
41. Roca O, Peñuelas O, Muriel A, García-de-Acilu M, Laborda C, Sacanell J, et al. Driving Pressure Is a Risk Factor for ARDS in Mechanically Ventilated Subjects Without ARDS. Respir Care 2021;66:1505-13.
42. Marini JJ, Crooke PS, Gattinoni L. Intra-cycle power: is the flow profile a neglected component of lung protection? Intensive Care Med 2021;47:609-11.
43. Young CC, Harris EM, Vacchiano C, Bodnar S, Bukowy B, Elliott RRD, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. Br J Anaesth 2019;123:898-913.
44. Arnal JM, Garnero A, Saoli M, Chatburn RL. Parameters for Simulation of Adult Subjects During Mechanical Ventilation. Respiratory Care 2018;63:158-68.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:420-424
DOI: 10.4274/BMJ.galenos.2021.2021.10-8

Research

Evaluation of S100B Protein in Patients with Schizophrenia with Seropositive and Seronegative Toxoplasma

Toxoplasma Seropozitif ve Seronegatif Şizofreni Hastalarında S100B Proteininin Değerlendirilmesi

Mustafa N. Namlı[1], Nuran Karabulut[2], Hakan Ayyıldız[3]

[1]Istanbul Health Directorate of Republic of Turkey Ministry of Health, Department of Public Inpatient Health Sevices 6rd, Istanbul, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Medical Virology, Istanbul, Turkey
[3]Elazığ Fethi Sekin City Hospital, Medical Biochemistry Laboratory Medical Biochemistry Laboratory, Medical BioMedical Biochemistry Laboratory Elazığ, Turkey

ABSTRACT

Objective: S100B is a calcium-binding protein that is secreted from astrocytes and other glial cells in the central nervous system and may affect the growth and/or differentiation of neurons and astrocytes. The neuropathological studies in cell cultures of *Toxoplasma gondii* and postmortem studies in patients with schizophrenia revealed many glial abnormalities, particularly in astrocytes. This study aimed to evaluate S100B protein levels in patients with schizophrenia having seropositive and seronegative toxoplasma.

Methods: This study included 40 patients with schizophrenia and 39 healthy control groups, with 20 toxoplasma seropositive in each group. The patients' psychopathology were evaluated with the positive and negative syndrome scale (PANSS). S100B level and *T. gondii* immunoglobulin G (IgG) were analyzed by electrochemiluminescence immunoassay and the enzyme-linked immune-sorbent assay method, respectively.

Results: No significant difference was found in S100B values between the patients with schizophrenia and healthy controls (p=0.94). No statistically significant correlations were found between S100B and both PANSS subscale scores and disease duration. S100B median values between toxoplasma IgG-positive and negative groups have no statistically significant difference in both healthy controls (p=0.38) and patients with schizophrenia (p=0.93).

Conclusion: This study found no association between S100B protein levels and both schizophrenia and latent toxoplasma. Some studies report a role for S100B in schizophrenia; however, uncertainties still exist and are in some ways contradictory.

Keywords: Schizophrenia, S100B, toxoplasma

ÖZ

Amaç: S100B, merkezi sinir sistemindeki astrositlerden ve diğer glial hücrelerden salgılanan, nöronların ve astrositlerin büyümesinde ve/veya farklılaşmasında rol oynayabilen kalsiyum bağlayıcı bir proteindir. *Toxoplasma gondii* hücre kültürlerinde yapılan nöropatolojik çalışmalarda ve şizofreni hastalarında yapılan postmortem çalışmalarda, özellikle astrositlerde olmak üzere birçok glial anormallik gösterilmiştir. Bu çalışmanın amacı, toksoplazma seronegatif ve seropozitif şizofreni hastalarında S100B protein düzeylerini değerlendirmekti.

Gereç ve Yöntem: Çalışmaya her grupta 20 toksoplazma seropozitif olmak üzere toplam 40 şizofreni hastası ve 39 sağlıklı kontrol grubu dahil edildi. Hastaların psikopatolojisi, pozitif ve negatif sendrom ölçeği (PANSS) ile değerlendirildi. S100B seviyesi ve *T. gondii* immünoglobulin (IgG), sırasıyla elektrokemilüminesans immünoassay yöntemi ve enzime bağlı immün-sorbent yöntemi ile analiz edildi.

Bulgular: Şizofreni hastaları ile sağlıklı kontroller arasında S100B değerlerinde anlamlı fark yoktu (p=0,94). S100B ile hem PANSS skorları hem de hastalık süresi arasında istatistiksel olarak anlamlı bir ilişki yoktu. Toxoplasma immünoglobulin G (IgG) pozitif ve negatif gruplar arasında S100B medyan değerlerinde hem sağlıklı kontrollerde (p=0,38) hem de şizofreni hastalarında (p=0.93) istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Bu çalışmada, S100B protein seviyeleri ile hem şizofreni hem de latent toksoplazma arasında bir ilişki bulunmamıştır. Bazı çalışmalar S100B'nin şizofrenide bir rolü olduğunu bildirmektedir, ancak bu konuda belirsizlikler hala mevcuttur ve bazı yönlerden çelişkilidir.

Anahtar Kelimeler: Şizofreni, S100B, toxoplasma

Address for Correspondence: Nuran Karabulut, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Medical Virology, Istanbul, Turkey
E-mail: nuranakarabulut@gmail.com ORCID ID: orcid.org/0000-0003-3550-2599

Cite as: Namlı MN, Karabulut N, Ayyıldız H. Evaluation of S100B Protein in Patients with Schizophrenia with Seropositive and Seronegative Toxoplasma. Med J Bakirkoy 2021;17:420-424

Received: 16.11.2021
Accepted: 06.12.2021

INTRODUCTION

The etiology of schizophrenia remains largely unclear and is believed to be multifactorial. In the past two decades, numerous studies have been conducted to find a direct link between latent toxoplasmosis and schizophrenia. *Toxoplasma gondii* is a common protozoan parasite that infects one-third of the world's population. Toxoplasma showing neurotropism is a parasite that migrates within the brain tissue, predominantly in the gray matter, localizing in neurons, astrocytes, and microglia. Its dormant form, the bradyzoite, can persist in the host brain for many years and perhaps until death (1,2).

Recently, numerous studies have suggested a link between schizophrenia and S100B protein. The S100 protein family that was described in the mid-1960s has been the subject of many studies in recent years. This protein family is called S100 since it is 100% soluble in ammonium sulfate and was originally purified from bovine brain and described as brain-specific (3). Currently, the S100 protein family consists of >20 calcium-binding proteins with structural similarities. Additionally, some members of the S100 protein family bind copper and/or zinc. S100B is secreted from many cells, i.e., astrocytes, oligodendrocytes, neurons, lymphocytes, or adipocytes. In physiological concentrations, S100B has neurotrophic and neuroprotective effects (4,5). However, overproduction of S100B can lead to neurotoxicity and inhibit the proliferation and differentiation of neurons, and it can induce neurodegeneration and apoptosis (6). S100B secretion is increased by pro-inflammatory cytokines and this protein could be involved in the unstable inflammatory response that is observed in various central nervous system disorders, including schizophrenia, Alzheimer's disease, and major depression (7). Therefore, measuring the functionality of astrocytes in patients with schizophrenia via the S100B protein, which can be detected in both serum and cerebrospinal fluid (CSF) is important. This study aimed to compare serum S100B levels in toxoplasma seronegative and seropositive schizophrenia cases.

METHODS

Participants

This study included 40 patients with schizophrenia and 39 healthy control groups, with 20 toxoplasma seropositive in each group. The clinical diagnosis of patients with schizophrenia was made through the Diagnostic and Statistical Manual of Mental Disorders. The positive and negative syndrome scale (PANSS) was used to measure the symptoms of patients with schizophrenia. Exclusion criteria included patients with a history of meningitis, encephalitis, mental retardation, head trauma, substance abuse, alcoholism, and immunodeficiency diseases. The control group consisted of 39 healthcare workers without a history of schizophrenia or psychiatric disorders. This study was approved by the Fırat University Ethical Committee (reference number: 08/12/26042016). The study was conducted following the Declaration of Helsinki.

Laboratory Analysis

Blood samples were obtained under sterile conditions from all study participants. Samples were stored at -20 °C until *T. gondii* IgG and S100B test analyses after centrifugation. All samples for *T. gondii* immünoglobulin (IgG) detection were analyzed using a commercial enzyme-linked immunosorbent kit (Vircell, Granada, Spain) on the Triturus system (Grifols, Parets del Valles, Spain) following the manufacturer's instructions. *T. gondii* IgG levels below 10 IU/mL were considered negative, and levels above 10 IU/mL were considered positive. Serum S100B level was analyzed by electrochemiluminescence immunoassay method on Cobas 8000/e602 analyzer (Roche Diagnostics, Risch Rotkreuz, Switzerland) using Roche kit. The S100B measuring range is between 0.005 µg/L and 39 µg/L.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 21.0 software (IBM Corp., Armonk, NY USA). The Kolmogorov Smirnov or Shapiro-Wilk test was used to determine the data normality distribution. Student's t-test or Mann-Whitney U test was used to compare continuous variables between the groups. The Chi-square test or Fisher's Exact test was used for categorical comparisons between the different groups. The Pearson correlation or Spearman's rho test was used to analyze the correlation between the parameters. The p-value of <0.05 was considered statistically significant.

RESULTS

This study included 40 patients with schizophrenia, 20 females and 20 males, with ages ranging between 22 and 54 years. The control group consisted of 39 healthy healthcare workers, 20 females and 19 males, with ages ranging between 24 and 56 years. No statistically significant difference was found between patients with schizophrenia and healthy controls in terms of age and gender (Table 1). Illness duration in schizophrenia cases ranged from 5 months to 31 years, and the median duration was 12 years.

The median S100B values that are detected in schizophrenia and healthy control groups are shown in Table 1. No

Table 1. Demographic, clinical, and laboratory characteristics of patients with schizophrenia and healthy controls

	Schizophrenia patients	Healthy controls	p
Number of participants	40	39	-
Age (mean ± SD)	38.70±8.36	38.97±8.11	0.88
Gender			
Male	20	19	0.91
Female	20	20	
T. gondii IgG positive, N	20	20	0.91
S100B, µg/L (median)	0.046	0.045	0.94
PANSS subscales			
Positive subscale score (median)	17	-	-
Negative subscale score (mean)	29.89±8.11	-	-
General psychopathology subscale score (mean)	37.22±14.45	-	-
PANSS total (median)	91.50	-	-

PANSS: Positive and negative syndrome scale, IgG: Immunoglobulin G, SD: Standard deviation

significant difference was found in S100B values between the two groups (p=0.94). No correlations were determined between S100B values and PANSS positive (r=0.24, p=0.15), PANNS negative (r=-0.11, p=0.52), general psychopathology (r=0.11, p=0.52), and PANNS total scores (r=0.26, p=0.12) in the patients. No significant correlation was determined between disease duration and S100B level (r=0.26, p=0.12).

Figure 1 shows healthy controls that were divided into two groups as Toxoplasma IgG positive and negative, in which S100B median value was higher in the positive group (0.047 µg/L) than in the negative group (0.042 µg/L), but this difference was not significant (p=0.38). Similarly, in patients with schizophrenia, S100B median values were 0.046 µg/L and 0.045 µg/L in Toxoplasma IgG-positive and negative groups, respectively, without a statistically significant difference (p=0.93).

DISCUSSION

S100B that has neurotrophic and neuroprotective effects is concentrated in astrocytes and other glial cell types, such as oligodendrocytes, Schwann cells, retinal Muller cells, ependymal cells, enteric glial cells, and certain subpopulations of neurons (5). S100B is thought to mediate interactions between the glial cells and between the neurons and glial cells, and it acts as a cytokine after being secreted from the glial cells (8,9).

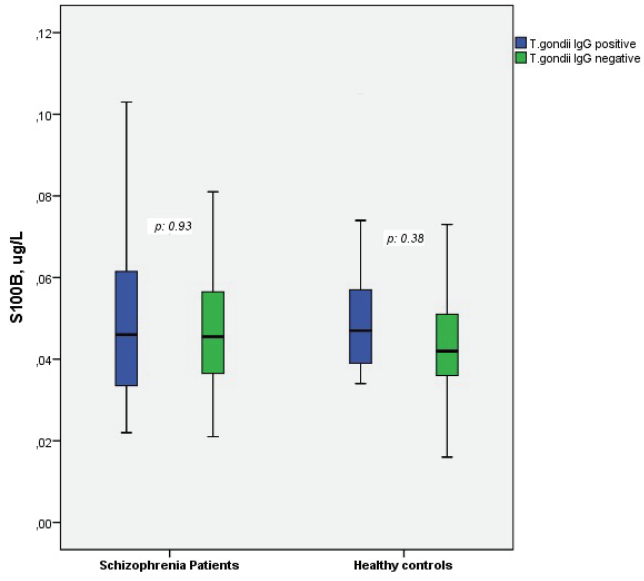

Figure 1. Comparison of S100B values in *Toxoplasma gondii* IgG positive and negative groups
IgG: Immunoglobulin G

Recently, various studies have suggested that the S100B protein is a biomarker of schizophrenia pathophysiology. Post mortem studies in patients with schizophrenia have shown that the S100 protein was upregulated in both the frontal cortex of patients with paranoid schizophrenia, but it was downregulated in the corpus callosum and deep white matter of the anterior cingulate gyrus (10-12). Previous studies that investigate the blood S100B levels in patients with schizophrenia revealed higher blood S100B levels in patients with schizophrenia than healthy control groups (8,13,14). Contrarily, a study reported no correlation between S100B and schizophrenia and another reported the decreased levels of S100B in schizophrenia (15,16). Additionally, serum S100B is reported to be elevated in drug-free and drug-naive patients with schizophrenia, and in the early phase of the disease (14,17). This study revealed no significant difference in S100B values between the schizophrenia and control groups. The study consisted of patients with chronic schizophrenia with median disease duration of 12 years, which may be a factor in the absence of a significant change in S100B values.

Data about S100B and psychopathology are controversial. A meta-analysis study revealed an inclusive relationship between S100B and psychopathology, whereas most studies did not find any relationship, and a negative correlation was found between PANNS negative and S100B, whereas a positive correlation in a few studies (7). This study revealed no significant correlation between the PANSS total or any PANSS subscale score and S100B.

A consensus was not determined on the effect of disease duration on S100B levels. Almost all studies reported no association between S100B concentrations and disease duration (9). Similarly, no relationship was also found between disease duration and S100B in this study. Only one study reported a negative correlation between S100B levels and disease duration (14).

Many studies reported a possible relationship between Toxoplasma and schizophrenia (18). *In vitro* neuropathological studies in cell cultures of *T. gondii* and post mortem studies on the brains of patients with schizophrenia revealed many glial abnormalities, particularly in astrocytes (19). No study has found a relationship between this parasite, which can remain dormant in the brain for years, and S100B, which shows the astroglial and microglial activation. This study found no significant difference was found between toxoplasma and S100B levels in both schizophrenia and healthy control groups.

Study Limitations

S100B could leak into the systemic circulation and CSF in the event of neuronal injury and blood-brain barrier disruption (20). CSF was not taken from the patients since it required an invasive procedure. Investigating the level of S100B in CSF instead of serum may be more valuable. The study population was relatively small, thus it should be repeated in the larger population.

CONCLUSION

Our study revealed no association between S100B protein levels and both schizophrenia and latent toxoplasma. The information regarding the behavior of this protein in the brain is lacking, thus uncertainties still exist and are in some ways contradictory.

ETHICS

Ethics Committee Approval: The study was approved by the Fırat University Ethical Committee (approval number: 08/12/26042016).

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

Authorship Contributions

Concept: M.N.N., N.K., Design: M.N.N., Data Collection or Processing: M.N.N., N.K., H.A., Analysis or Interpretation: M.N.N., N.K., H.A., Literature Search: N.K., H.A., Writing: M.N.N., N.K.

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

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

REFERENCES

1. Chaudhury A, Ramana BV. Schizophrenia and bipolar disorders: The Toxoplasma connection. Trop Parasitol 2019;9:71-6.
2. Xiao J, Prandovszky E, Kannan G, Pletnikov MV, Dickerson F, Severance EG, et al. Toxoplasma gondii: Biological Parameters of the Connection to Schizophrenia. Schizophr Bull 2018;44:983-92.
3. Moore BW. A soluble protein characteristic of the nervous system. Biochem Biophys Res Commun 1965;19:739-44.
4. Kozłowska E, Brzezińska-Błaszczyk E, Agier J, Wysokiński A, Żelechowska P. Alarmins (IL-33, sST2, HMGB1, and S100B) as potential biomarkers for schizophrenia. J Psychiatr Res 2021;138:380-7.
5. Michetti F, D'Ambrosi N, Toesca A, Puglisi MA, Serrano A, Marchese E, et al. The S100B story: from biomarker to active factor in neural injury. J Neurochem 2019;148:168-87.
6. Van Eldik LJ, Wainwright MS. The Janus face of glial-derived S100B: beneficial and detrimental functions in the brain. Restor Neurol Neurosci 2003;21:97-108.
7. Aleksovska K, Leoncini E, Bonassi S, Cesario A, Boccia S, Frustaci A. Systematic review and meta-analysis of circulating S100B blood levels in schizophrenia. PLoS One 2014;9:e106342.
8. Qi LY, Xiu MH, Chen DC, Wang F, Kosten TA, Kosten TR, et al. Increased serum S100B levels in chronic schizophrenic patients on long-term clozapine or typical antipsychotics. Neurosci Lett 2009;462:113-7.
9. Yelmo-Cruz S, Morera-Fumero AL, Abreu-González P. S100B and schizophrenia. Psychiatry Clin Neurosci 2013;67:67-75.
10. Steiner J, Bernstein HG, Bielau H, Farkas N, Winter J, Dobrowolny H, et al. S100B-immunopositive glia is elevated in paranoid as compared to residual schizophrenia: a morphometric study. J Psychiatr Res 2008;42:868-76.
11. Steiner J, Schmitt A, Schroeter ML, Bogerts B, Falkai P, Turck CW, et al. S100B is downregulated in the nuclear proteome of schizophrenia corpus callosum. Eur Arch Psychiatry Clin Neurosci 2014;264:311-6.
12. Katsel P, Byne W, Roussos P, Tan W, Siever L, Haroutunian V. Astrocyte and glutamate markers in the superficial, deep, and white matter layers of the anterior cingulate gyrus in schizophrenia. Neuropsychopharmacology 2011;36:1171-7.
13. Deng H, Kahlon RS, Mohite S, Amin PA, Zunta-Soares G, Colpo GD, et al. Elevated Plasma S100B, Psychotic Symptoms, and Cognition in Schizophrenia. Psychiatr Q 2018;89:53-60.
14. Lara DR, Gama CS, Belmonte-de-Abreu P, Portela LV, Gonçalves CA, Fonseca M, et al. Increased serum S100B protein in schizophrenia: a study in medication-free patients. J Psychiatr Res 2001;35:11-4.
15. Uzbay T, Goktalay G, Kayir H, Eker SS, Sarandol A, Oral S, et al. Increased plasma agmatine levels in patients with schizophrenia. J Psychiatr Res 2013;47:1054-60.
16. Gattaz WF, Lara DR, Elkis H, Portela LV, Gonçalves CA, Tort AB, et al. Decreased S100-beta protein in schizophrenia: preliminary evidence. Schizophr Res 2000;43:91-5.
17. Chen S, Tian L, Chen N, Xiu M, Wang Z, Yang G, et al. Cognitive dysfunction correlates with elevated serum S100B concentration in drug-free acutely relapsed patients with schizophrenia. Psychiatry Res 2017;247:6-11.

18. Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr Bull 2007;33:729-36.
19. Yuksel P, Alpay N, Babur C, Bayar R, Saribas S, Karakose AR, et al. The role of latent toxoplasmosis in the aetiopathogenesis of schizophrenia--the risk factor or an indication of a contact with cat? Folia Parasitol (Praha) 2010;57:121-8.
20. Moss BP, Patel DC, Tavee JO, Culver DA. Evaluating S100B as a serum biomarker for central neurosarcoidosis. Respir Med 2020;162:105855.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:425-431
DOI: 10.4274/BMJ.galenos.2021.2021.10-2

Research

Evaluation of Brain Death in Children in a Tertiary Pediatric Intensive Care Unit

Üçüncü Basamak Pediatrik Yoğun Bakım Ünitesindeki Çocuklarda Beyin Ölümünün Değerlendirilmesi

Süleyman Bayraktar[1], Bilge Tanyeri-Bayraktar[2], Murat Elevli[3]

[1]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, Istanbul, Turkey
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Neonatology, Istanbul, Turkey
[3]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic Pediatrics, Istanbul, Turkey

ABSTRACT

Objective: This study aimed to evaluate the characteristics of children who are diagnosed with brain death (BD) in a tertiary care pediatric intensive care unit (PICU) and highlight the organ donation rates.

Methods: A retrospective observational study was conducted among pediatric patients who met the criteria of BD based on the medical records in all deaths that occurred between January 2018 and May 2021. The demographic data, main BD cause, duration between admission to PICU and BD decision, length of stay, time between BD decision and cardiac arrest, presence of apnea and ancillary tests, and organ donation status were recorded.

Results: This study analyzed 642 patients who are admitted to the PICU, wherein 1.9% was diagnosed as BD. Asphyxia was the most frequent cause of BD (33.3%). The mean interval between the suspected of BD diagnosis and median of duration between BD decision and cardiac arrest were 18.58±13.77 (min: 3, max: 48) h and 36 (minimum (min): 1, maxsimum (max): 192) h, respectively. The mean length of stay in the PICU was 16.75±11.36 days (min: 3, max: 42). The disorders related to BD include diabetes insipidus (58.3%) and hypothermia (33.3%). Apnea test was positive in 6 (50%) of 12 children. At least one ancillary test was used in all patients. Five of 12 (41.7%) patients were not eligible for organ donation because they were refugee, and the families of the remaining 7 patients did not give permission for organ donation.

Conclusion: Organ donation can be increased if frequent family meetings are held by an experienced and trained team coordinator, including psychologists and religious authorities. This issue can be organized as a certified and standardized program throughout the country.

Keywords: Brain death, children, pediatric intensive care unit, organ donation, refugee

ÖZ

Amaç: Üçüncü basamak çocuk yoğun bakım ünitesinde (YBÜ) beyin ölümü (BÖ) tanısı alan çocukların özelliklerini değerlendirmek ve organ bağışı oranlarına vurgu yapmak.

Gereç ve Yöntem: Ocak 2018-Mayıs 2021 tarihleri arasında meydana gelen tüm ölümlere ilişkin tıbbi kayıtlara dayanarak, BÖ kriterlerini karşılayan çocuk hastalarda geriye dönük gözlemsel bir çalışma yapılmıştır. Demografik veriler, BÖ'nün ana nedeni, çocuk YBÜ'ne kabul ve BÖ kararı arasındaki süre, hastanede kalış süresi, BÖ kararı ile kardiyak arrest arasındaki süre, apne testi ve yardımcı testlerin varlığı, organ bağış durumu kaydedildi.

Bulgular: Çocuk YBÜ'ye başvuran toplam 642 hastanın %1,9'u BÖ tanısı aldı. BÖ'nün en sık nedeni asfiksi idi (%33,3). BÖ şüphesi ve BÖ tanısı arasındaki sürenin ortalama değeri ve BÖ tanısından sonra kardiyak arrestin meydana gelmesi arasındaki sürenin ortanca değerleri sırasıyla 18,58±13,77 [(minimum (min): 3, maksimum (maks): 48)] saat ve 36 (min: 1, maks: 192) saat idi. Çocuk YBÜ'de ortalama kalış süresi 16,75±11,36 gün (min: 3, maks: 42) idi. BÖ'ye bağlı bozukluklar diabetes insipidus (%58,3) ve hipotermi (%33,3) idi. Oniki çocuğun 6'sında (%50) apne testi pozitifti. Tüm hastalarda en az bir yardımcı test kullanıldı. On iki hastadan 5'i (%41,7) mülteci oldukları için organ bağışına uygun bulunmadı, kalan 7 hastanın aileleri ise organ bağışına izin vermedi.

Address for Correspondence: Süleyman Bayraktar, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, Istanbul, Turkey
Phone: +90 532 385 10 78 E-mail: bsuleyman@hotmail.com ORCID ID: orcid.org/0000-0002-8080-2438

Cite as: Bayraktar S, Tanyeri-Bayraktar B, Elevli M. Evaluation of Brain Death in Children in a Tertiary Pediatric Intensive Care Unit. Med J Bakirkoy 2021;17:425-431

Received: 09.10.2021
Accepted: 17.11.2021

Sonuç: Psikologlar ve dini otoritelerin de dahil olduğu, deneyimli ve eğitimli bir koordinatör ekip tarafından, sık sık aile toplantıları yapılırsa organ bağışı artırılabilir. Bu konu ülke genelinde sertifikalı ve standartlaştırılmış bir program olarak düzenlenebilir.

Anahtar Kelimeler: Beyin ölümü, çocuklar, çocuk yoğun bakım ünitesi, organ bağışı, göçmen

INTRODUCTION

Brain death (BD) is a clinical diagnosis that is characterized by the complete, permanent, and irreversible loss of all brain, brainstem, and cerebellar activities (1-3). According to the Turkish Neurological Society, BD is described as "whole BD" that refers to the medical death state (4). The pathophysiologic features of BD include increased intracranial pressure, disrupted cerebral blood flow, and occluded cerebral perfusion (1,3).

The American Academy of Pediatrics, the Child Neurology Society, and the Society of Critical Care Medicine published the BD guidelines in children (5,6). Due to insufficient globally accepted definition and formal declaration guidelines, avoidance, and concerns continue in BD decisions in the pediatric intensive care units (PICU) (7). However, as access to critical care increases, more practitioners encounter this difficult clinical scenario (8). In this setting, the incidence of reported BD varies. The reported rates of BD are found in a wide range (10.8%-37%) in different pediatric studies (9-14).

Early diagnosis of BD is crucial for organ and tissue protection from cardiovascular and metabolic changes for organ donors (3,11). Turkey was one of the first countries to legally establish the guidelines of BD; however, approximately 11,932 patients are waiting for organ transplantation and 5%-13% of them are pediatric patients (15).

Today, studies that conducted diagnosis of BD and the subsequent processes in children are limited. Thus, this study aimed to analyze the characteristics of children who are diagnosed with BD and highlight the organ donation rates in the PICU.

METHODS

Study Design

This retrospective observational study was conducted among pediatric patients who met the criteria for BD between January 2018 and May 2021. The pediatric ICU at University of Health Sciences Turkey, Haseki Training and Research Hospital is a tertiary care facility that is located in a low socioeconomic and cosmopolitan place of Istanbul. While our unit has 6 beds until April 2019, it has been increased to 10 beds after this date.

BD Evaluation Policy

Declaration of BD in pediatric cases is a special issue in Turkey, as well as worldwide (16). According to the Regulations on Organ and Tissue Transplantation Services (17) in Turkey, the process in pediatric cases is as follows: a clinical BD finding should be established to fulfill the non-reversibility criteria. At the end of the waiting period, a second examination is required to confirm the unchanged clinical BD findings and a single apnea test is sufficient for diagnosis during this process.

The waiting period is 48 h in infants up to 2 months old, 24 h between 2 months and 1 year old, 12 h in >1 year, and 24 h in anoxic BD. Therefore, experienced pediatric radiologists who can perform and evaluate tests that show cerebral blood flow can facilitate a faster BD diagnosis without waiting for re-examination of brain stem reflexes (4). The guideline on BD that was published by the Turkish Neurological Association stated that at least two confirmatory tests in the newborn group (up to 2 months) and one laboratory test in children aged >2 months are required (4).

The decision of BD was taken with the judgment of two physicians following the Turkish BD regulation (16).

Apnea Test

The apnea test objectively measures the brainstem function without the respiratory drive that support BD declaration (18). Apnea testing standards also differ among countries, both in duration (5 to 15 min) and interpretation of objective arterial blood gases (no pH guidelines for <7.4) (13,18).

The apnea test was performed by a pediatric intensivist in the PICU and was interpreted as the absence of spontaneous breathing with partial pressure of carbon dioxide ($PaCO_2$) of >60 mmHg (or a 20 mmHg increase in $PaCO_2$ over the normal $PaCO_2$ baseline) and the corresponding decrease in pH before buffering mechanisms can occur. Without observed respiratory efforts during the test, the apnea test demonstrates an insufficient drive to breathe, hence absence of function of the medullary respiratory centers. In the presence of hypoxia or hypotension during the testing, which makes the test invalid, the test should be stopped and the hypoxia or hypotension should be corrected (13).

Ancillary Tests

Uncompleted clinical examination or the apnea test, concerns about the validity of clinical findings, and desire to shorten the observation period between examinations are the indications of using ancillary tests (19). Ancillary tests assess for brain function [electroencephalogram (EEG)] or cerebral blood flow (radionuclide imaging, angiography,

etc.) in the BD diagnosis (18). The term "ancillary" is preferred to "confirmatory," nevertheless, they can assist the clinician in BD diagnosis. Generally, ancillary tests are mandatory in BD diagnosis in some countries (10). Ancillary tests that are used in our hospital were EEG, computed tomography angiography (CTA), and transcranial Doppler sonography (TDS).

Declaration of BD to the Family

As soon as the diagnosis is made, BD declaration should be announced to the family and the organ transplant coordinator should be notified. These procedures were applied for all cases in the present study. According to the relevant law, BD was firstly declared to parents by the PICU team. After that, the hospital's local organ transplant coordinator interviews the families for organ donation.

Ethical Approval and Data Selection

The Local Ethical Board of University of Health Sciences Turkey, Haseki Training and Research Hospital approved the study (approval no: 61-2021 date: 14.07.2021).

The medical records of patients were accessed using the hospital database. The following demographics were recorded: age at diagnosis, sex, main BD cause, and duration between admission to PICU and BD decision, length of stay, interval between BD decision and cardiac arrest, and organ donation status.

The main cause to BD was grouped into the following categories: Multiple trauma, central nervous system (CNS) infection, hypoxia/asphyxia (status epilepticus, following cardiopulmonary arrest, sudden death, etc.), stroke, and CNS tumor.

Alterations accompanying to BD were analyzed, such as diabetes insipidus, hypothermia, hyperglycemia, coagulopathy, and hemodynamic instability.

Diabetes insipidus: Polyuria (urine output of >4 mL/kg/h for children and 300 mL/h for children >70 kg), urine density of <1.005, high serum osmolality (>300 mOsm/kg) and low urine osmolality (<300 mOsm/kg) at the time of diagnosis, and hypernatremia with Na of >145 mEq/dL.

Hypothermia: Core temperature of <35°C

Hyperglycemia: Blood glucose of >180 mg/dL

Coagulopathy: Prothrombin time of <60%

Hemodynamic dysfunction: Mean blood pressure of <2 standard deviations (SD) from the 50th percentile for the age and/or inotrope or vasopressor requirements or increased dosage

All patients were eligible for organ donation; however, five of them were refugees.

Statistical Analysis

The results were analyzed using the Statistical Package for the Social Sciences statistical software program (version 18.0, SPSS Inc. IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as frequency and percentage values for categorical variables and mean ± SD (min, max) for continuous variables. If the measured outcome distribution based is abnormal, values were expressed as median and interquartile range.

RESULTS

Totally, 642 patients were followed up in the PICU, where 50 (7.8%) died. Of the 50, 12 (24.0%) were diagnosed with BD. Of all PICU admissions, 1.9% were diagnosed with BD. The demographic and clinical findings were presented in Table 1. The mean age of patients was 6.7±3.8 years [minimum (min): 4 months, maksimum (maks): 11.5 years]. Of the children, 58.3% (n=7) were girls. The causes of BD were listed as asphyxia in 4 (33.3%), CNS tumor in 3 (25.0%), CNS infections in 3 (25.0%), and trauma in 2 (16.7%) patients. The suspected of BD to BD diagnosis and the median duration of cardiac arrest after diagnosis were 18.58±13.77 (min: 3, max: 48) h and 36 (min: 1, max: 192) h, respectively. The mean length of stay in the PICU was 16.75±11.36 days (min: 3, max: 42). The disorders related to BD include diabetes insipidus (58.3%) and hypothermia (33.3%). Apnea test was positive in 6 (50%) of 12 children. During apnea test one patient had pneumothorax. Eight (66.7%) children were followed with EEG, which revealed isoelectrical activity. Ten (83.3%) children had CTA and only 2 (16.7%) patients had TDS. Both the ancillary tests were compatible with BD. All cases were suitable for organ donation. Since 5 patients are refugees, they were accepted as unsuitable for organ donation. The families refused organ transplantation in 7 patients. The main reasons for the rejection of organ donation were religious beliefs in 5 (71.4%) families and the inability to accept the beating of the heart as dead in 2 (28.6%) families.

DISCUSSION

This retrospective study found the rate of BD as 24.0% among patients who died in the PICU, and suitable donors were found for organ donation; however, no family consent could be obtained.

Bonetto et al. (10) reported the overall mortality as 7.45% and BD as 19.14%. Kirschen et al. (9) declared the rate of

Table 1. Demographic and clinical features of children diagnosed with BD

Patient no	Age (year)	Sex	Cause of BD	Length of stay (d)	Time to diagnosis of BD (h)	Time of cardiac arrest after BD (h)	Apnea test	Ancillary tests	Complications	Suitability for organ donation	Organ donation
1	11.5	M	Traumatic brain injury	42	28	36	Positive	EEG	Hypothermia, diabetes insipidus	Suitable	None
2	10.5	M	Optic glioma	27	6	12	Inconclusive	EEG, CTA	-	Suitable	None
3	10	F	Encephalitis	28	8	168	Positive	EEG, CTA	Hypothermia	Suitable	None
4	7.5	F	Pons glioma	4	6	36	Positive	CTA	-	Suitable	None
5	7.5	F	Asphyxia, epilepsia	3	3	1	Inconclusive	CTA	Hypothermia, diabetes insipidus, pneumothorax	Suitable	None (Syrian)
6	11	F	Traumatic brain injury	10	16	192	Positive	EEG	Diabetes insipidus	Suitable	None
7	6	M	Menengitis (Tbc)	23	11	11	Positive	EEG, CTA, TDS	Hypothermia, diabetes insipidus	Suitable	None (Georgian)
8	8	M	Encephalitis	13	48	32	Inconclusive	CTA	-	Suitable	None (Syrian)
9	2.5	F	Atypical rhabdoid tumor	17	12	48	Inconclusive	EEG, CTA	Diabetes insipidus	Suitable	None
10	0.4	F	Asphyxia, post arrest	14	35	48	Inconclusive	EEG, CTA	Hypothermia, diabetes insipidus	Suitable	None
11	3.5	M	Asphyxia, post arrest	11	26	26	Inconclusive	CTA, TDS	Diabetes insipidus	Suitable	None (Syrian)
12	2.5	F	Asphyxia, post arrest	9	24	44	Inconclusive	EEG, CTA	Hypothermia	Suitable	None (Iraqi)

BD: Brain death; M: Male; F: Female; EEG: Electroencephalogram; CTA: Computed tomography angiography; TDS: Transcranial Doppler sonography

BD as 20.7%. The crude rate of BD was 1.1% in the PICU from our country (20). Sucu et al. (1) noticed the mortality as 10.2% and the BD as 17% of these patients. Yener et al. (11) mentioned 10.8% of deaths as BD. Our BD percentage was found to be similar to the previous studies.

A study conducted in children revealed the average age as 6.8±5.5 years (21). Kirschen et al. (9) reported that the age of patients in this group was between 2 and 12 years. The mean age of children in our study was consistent with the study of Özmert et al. (21).

The major disease that causes BD varied in studies. The most common causes of BD include hypoxic-ischemic injury, shock, and/or respiratory arrest, and traumatic brain injury (9,12,22). Some studies have classified the common diseases of BD according to the age of children. Multiple trauma was found as the main cause at median 7 years old (10), whereas traumatic brain injury was the leading cause of BD in children over 1 year old in developed countries, and no clear data is reported on this subject in our country (1). Trauma and intracranial hemorrhage were found as the highest rate in patients who are diagnosed with BD in some studies (2,6,21). A study conducted in our country revealed that traumatic brain injury was the leading cause in 70% of patients (20). Thus, Sucu et al. (1) stated that traumatic brain injury was a cause at a rate of 7%. Contrarily, Yener et al. (11) found post-cardiorespiratory arrest as a common cause of BD. Our study found that the most common reason was asphyxia (33.3%) and the diagnosis of patients at admission

varied in a large spectrum.

Early recognition of BD in hospital follow-up is important in evaluating the patients for organ donation (23). The mean time to diagnosis after BD suspicion was 5.9±6.2 days in a study by Özmert et al. (21), whereas another study mentioned 3 days (24). Karasu et al. (25) reported that these periods were 6.8 days in patients aged 18 years. Additionally, Altınsoy et al. (26) compared two different time periods and found that duration of BD diagnosis shortened over the years. In previous studies, the time of BD diagnosis was not found to be different in children compared with adults. Our study revealed that the time of diagnosis was 18.58 hours, which was shorter than the reported studies because of not waiting for the second examination.

The studies also reported the interval from BD diagnosis to cardiac death, which revealed 6.8 days in patients younger than 18 years of age and 2.5 days in patients aged 18 years and older (25) since the time for cardiac death lasts longer than expected because physicians tend to continue life support both for cultural reasons, while getting the decision of BD from the families and change their minds for organ donation idea (27). The mean time to develop cardiac arrest after the diagnosis of BD was 6.9±7.4 days in non-donor cases whose medical support had been reduced (21). The duration of cardiac arrest after diagnosis was similar in both children (3.63±4.93 days) and adults (2.17±2.31 days) (26). Our study revealed that the median interval between BD and cardiac arrest was 36 h.

The most common alterations reported in studies include hypothermia, diabetes insipidus, and hemodynamic dysfunction (10,11,21). Antidiuretic hormone deficiency occurs in 65%-90% of patients with BD due to neurohypophysis damage (20). Bonetto et al. (10) also found hemodynamic dysfunction (63.2%) and diabetes insipidus (46.6%) in their study. A careful organ preservation treatment protocol in intensive care is the first step in successful organ transplantation. Therefore, knowing and addressing the mechanisms of complications is important (21). In our patients, hypothermia and diabetes insipidus were obtained in accordance with the literature.

Apnea test is mandatory in BD diagnosis in Turkey; however, Sucu et al. (1) found positive apnea test in 36% of patients. Our study applied the apnea test to all of patients, but was terminated due to complications (hypoxia, hypotension, etc.) in 50%. Positive apnea test was found higher in our study than the study of Sucu et al. (1). The reasons behind low apnea testing in some countries are as follows: 1. It is invasive and risky 2. Obtaining consent form from the guardians is difficult (7). Our country does not mandate taking a consent form for an apnea testing. During the apnea test, serious complications (cardiac arrest, hypotension, hypoxemia, and pneumothorax) may occur (28,29). One patient had pneumothorax during the apnea test.

The clinical evaluation is prioritized over the ancillary tests according to the pediatric BD guidelines that was revised in 2011, but a variety of ancillary tests are currently used in clinical practice (10,19,29). Studies showed that healthcare professionals used more ancillary tests in pediatric patients than in adults (19). The idea behind this behavior may be an attempt to objectively demonstrate the absence of cerebral blood flow or electrical brain function, rather than findings that appear subjective on clinical examination (19). BD declaration using ancillary methods is mandatory in Argentina (10). The consequences of adopting a health policy in the mandatory ancillary methods are based on the ethical and cultural conditions specific to each country. A study conducted in our country revealed that 76.2% of patients needed ancillary tests, the most common was CTA (22.4%) and mentioned that the need for ancillary tests declined throughout the years because of awareness and clinical experience of involved physicians (27). Özmert et al. (21) reported that EEG was performed in 61% of patients in addition to the apnea test. They used radiological imaging methods in 39% of patients (21). Another study by Altınsoy et al. (26) used DSA to support the diagnosis of BD and mentioned that DSA was the gold standard in BD diagnosis and might contribute to shortening the diagnosis period (26). Karasu et al. (25) showed that 30.4% of BD cases needed ancillary tests for diagnosis. In our study, the ratio of the ancillary tests performed seemed higher than the other studies to convince the families in BD decision. In our hospital region, the educational level of population is low, thus they rely on sophisticated diagnostic tools. They have no idea about BD. The term BD is a traumatic diagnosis for families who face it for the first time in their lives. BD is often confused with the diagnosis of vegetative life. Socio-cultural structure, religious beliefs, influence of family elders, and being a refugee are the factors effecting family reactions. Efforts should be made to improve the society's understanding of BD and to improve physician practices in determining BD (19). However, the diagnosis and process of BD is difficult in pediatric patients, especially in patients with hemodynamic disorders, thus physicians may act more cautiously.

In the field of pediatrics, the need for solid organ donations has increased worldwide, 1.5%-2% patients were in the waiting list of developed countries (21). Organ donation rate was found in 43.8 people per million in Spain (30). A

retrospective adult study in Qatar reported the rate of family rejection as 93%. This result was attributed to various factors, such as religious beliefs, culture, population dynamics (high number of immigrants), and ignorance of the importance of organ donation (31). Another study included 268 patients with a family approval rate of 78.4% and the organ donation approval rate rose with the increased frequency of meetings held by an organ transplantation coordinator with the family after BD declaration (32). Organ transplant centers and physicians in our country are adequately equipped; however, the number of organ donations is insufficient. The trained physicians, standardization of BD protocols, use of a checklist, and frequent meetings with families using precise, consistent, and clear language are important to ensure the integrity of BD determination and organ donation (9,32). Battal et al. (24) found the rate of organ donation as 29.03% in their study, whereas other studies reported 17%-34.2% (21,25,27). The rate of organ donation is still less than expected, and many patients are on transplant waiting lists (27). A study conducted in PICU revealed that no donor was issued like our study (1). Previous studies stated that the most serious problem regarding organ donation in Turkey was the death of patients without BD diagnosis and the lack of organ transplant coordinators (2). Recently, the use of international guidelines and the organization of the intensive care team enabled early BD diagnosis, but the organ donation rate is still low. When interviewed with the families of organ donors, Kıraklı et al. (33) reported that 36% of them seemed previously positive, and 64% attributed this to the influence of the coordinator. Altınsoy et al. (26) revealed that the rate of organ donation was 37.87% before 2014 and 21.15% after 2014. They commented that this difference may be due not only to be social characteristics of the guardian of patients but also to the communication skills of the employees in the organ donation coordination unit (26). Therefore, organ transplant coordinators, who will receive family approval, should be trained and experienced. Family interviews that are conducted by an experienced and trained transplant coordinator should emphasize that BD is a real death and organ donation is important. Religious, cultural, and legal reasons and the lack of adequate infrastructure and resources are the main reasons behind the continuation of life-saving and life-improving treatment and rejection of organ donation. Some physicians reported that it is commonly requested to continue organ support because of the belief that a patient who is declared BD can regain neurological function or a lack of acceptance that a person can be dead if the heart was still beating (9). Another obstacle to organ donation in our study was being a refugee. According to the organ transplant regulation, the inability to receive organ donations from refugees reduces the rate of organ transplants, as seen in our study.

Study Limitations

The study was conducted in a retrospective design. The results are from a single center of 10-bed PICU, thus the size of the study may be too small.

CONCLUSION

Families should be informed that BD is considered a definite death and that organ donation is important. In this respect, the importance of informing the public, regularly through the media, and social media was emphasized. Having a psychologist who is experienced as an organ donation coordinator and can properly communicate with families will increase the rate of organ donation. The donation rate is believed to increase if family meetings are frequently held by an experienced and trained coordinator team including religious authorities. This issue can be organized as a certified and standardized program throughout the country. Shortly, organ donation rates can be increased by designing the regulations about refugees becoming organ donors.

ETHICS

Ethics Committee Approval: The Local Ethical Board of University of Health Sciences Turkey, Haseki Training and Research Hospital approved the study (approval no: 61-2021 date: 14.07.2021).

Informed Consent: This study is retrospective.

Authorship Contributions

Surgical and Medical Practices: S.B., M.E., Concept: S.B., B.T.B., Design: S.B., B.T.B., Data Collection or Processing: S.B., Analysis or Interpretation: S.B., B.T.B., M.E., Literature Search: S.B., B.T.B., Writing: S.B., B.T.B., M.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. Sucu A, Tolunay O, Çelik T, Kahveci B, Celiloğlu C, Özdemir U, et al. Evaluation of Patients Diagnosed with Brain Death in Pediatric Critical Care. J Pediatr Emerg Intensive Care Med 2018;5:59-63.
2. Atik B, Kılınç G, Atsal AÖ, Çöken F, Yarar V. Our Brain Death and Organ Donation Experience: Over 12 Years. Transplant Proc 2019;51:2183-5.
3. Anıl AB, Anıl M, Yavaşcan Ö, Kanar B, Aksu N. Brain Death and Organ Transplantation in Children: A Case Report. Journal of Child 2009;9:195-8.

4. Turkish Neurological Society - Diagnostic Guidelines for Brain Death. Turk J Neurol. 2014;20:101-4.
5. Nakagawa TA, Ashwal S, Mathur M, Mysore M; Society of Critical Care Medicine, Section on Critical Care and Section on Neurology of American Academy of Pediatrics; Child Neurology Society. Clinical report-guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics 2011;128:720-40.
6. Mathur M, Ashwal S. Pediatric brain death determination. Semin Neurol 2015;35:116-24.
7. Araki T, Yokota H, Fuse A. Brain Death in Pediatric Patients in Japan: Diagnosis and Unresolved Issues. Neurol Med Chir (Tokyo) 2016;56:1-8.
8. Wooldridge G, Fonseca Y. Confirming Pediatric Brain Death in resource-limited settings: Lessons and challanges. Pediatr Neurol 2020;111:85-6.
9. Kirschen MP, Francoeur C, Murphy M, Traynor D, Zhang B, Mensinger JL, et al. Epidemiology of Brain Death in Pediatric Intensive Care Units in the United States. JAMA Pediatr 2019;173:469-76.
10. Bonetto G, Taffarel P, Gamerman M, Jorro Barón F, Gaviña C, Flores L, et al. Brain death and organ donation in Argentine pediatric intensive care units. A multicenter study. Arch Argent Pediatr 2018;116:54-60.
11. Yener N, Paksu MŞ, Köksoy Ö. Brain Death in Children: Incidence, Donation Rates, and the Occurrence of Central Diabetes Insipidus. J Crit Care Med (Targu Mures) 2018;4:12-6.
12. Lago PM, Piva J, Garcia PC, Roster E, Bousso A, Sarno MO, et al. Brain death: medical management in seven Brazilian pediatric intensive care units. J Pediatr (Rio J) 2007;83:133-40.
13. Joffe AR, Shemie SD, Farrell C, Hutchison J, McCarthy-Tamblyn L. Brain death in Canadian PICUs: demographics, timing, and irreversibility. Pediatr Crit Care Med 2013;14:1-9.
14. Goh AY, Mok Q. Clinical course and determination of brainstem death in a children's hospital. Acta Paediatr 2004;93:47-52.
15. Gündüz RC, Şahin Ş, Uysal-Yazıcı M, Ayar G, Yakut Hİ, Akman AÖ, et al. Brain death and organ donation of children. Turk J Pediatr 2014;56:597-603.
16. Sağlık bakanlığı ve bağlı kuruluşların teşkilat ve görevleri hakkında kanun hükmünde kararname ile bazı konularda değişiklik yapılmasına dair kanun. 2014. Available from: http://www. resmigazete.gov. tr/eskiler/2014/01/20140118-1.htm (accessed 27.1.2014 2014) 6.
17. Organ ve Doku Alınması Saklanması ve Nakli Hakkında Kanun (29.05.1979 Sayısı: 2238 R.G. Tarihi: 03.06.1979 R.G. Sayısı: 16655). 1979. Available from: http://www.saglik. gov.tr/TR/belge/1-445/tarihi29051979-sayisi2238-rg-tarihi03061979-rg-sayis-html (accessed 22.12.2013 2013).
18. Rayner M, Mansoor M, Holt T, Hansen G. Brain Death Criteria: Medical Dogma and Outliers. Yale J Biol Med 2019;92:751-5.
19. Lewis A, Adams N, Chopra A, Kirschen MP. Use of Ancillary Tests When Determining Brain Death in Pediatric Patients in the United States. J Child Neurol 2017;32:975-80.
20. Öztürk NY, İnceköy Girgin F, Birtan D, Cinel İ. Exploring brain death at a tertiary pediatric intensive care unit in Turkey; Incidance, etiology and organ donation. J Pediatr Emerg Intensive Care Med. 2016;3:11-4.
21. Özmert S, Sever F, Ayar G, Yazıcı MU, Öztaş DK. Brain Death and Organ Donation in Paediatric Intensive Care Unit. Turk J Anaesthesiol Reanim 2019;47:55-61.
22. Gotay-Cruz F, Fernández-Sein A. Pediatric experience with brain death determination. P R Health Sci J 2002;21:11-5.
23. Gómez MP, Arredondo E, Páez G, Manyalich M. International registry in organ donation and transplantation 2010. Transplant Proc 2012;44:1592-7.
24. Battal M, Horoz A, Karatepe O, Çitgez B. Experience of research hospital in determination of brain death. Med Bull Sisli Etfal Hosp 2013;47:59-62.
25. Karasu D, Yılmaz C, Karaduman İ, Çınar YS, Büyükkoyuncu Pekel N. Retrospective Analysis of Patients with Brain Death. J Crit Intensive Care 2015;6: 23-6.
26. Altınsoy S, Özdemir EŞ, Baran İ, Akelma FK, Arslan MT, Ergil J. Evaluation of Patients with Brain Death Diagnosis and Investigation of the Effect of New Regulation on the Duration of Diagnosis. J Turk Intens Care 2020;18:21-7.
27. Mutlu NM, Peker TT, Acar S, Koca B, Soyal ÖB, Titiz AP, et al. Brain Deaths and Donors in an Education and Research Hospital. Transplant Proc 2019;51:2176-9.
28. Thery G, Rosman J, Julien G, Chaix F, Mateu P. Brain death: Bilateral pneumothorax and pneumoperitoneum after an apnoea test. Anaesth Crit Care Pain Med 2019;38:89-90.
29. Monteiro LM, Bollen CW, van Huffelen AC, Ackerstaff RG, Jansen NJ, van Vught AJ. Transcranial Doppler ultrasonography to confirm brain death: a meta-analysis. Intensive Care Med 2006;32:1937-44.
30. Statista. Rates of deceased organ donors in select countries in 2017 (per million population). 2017. accessed, https://www.statista. com/statistics/406893/rate-of-organ-donation-by-deceased-donorsin-select-countries
31. George S, Thomas M, Ibrahim WH, Abdussalam A, Chandra P, Ali HS, et al. Somatic survival and organ donation among brain-dead patients in the state of Qatar. BMC Neurol 2016;16:207-11.
32. Frutos MA, Blanca JM, Mansilla JJ, Rando B, Ruiz P, Guerrero F, et al. Organ donation: a comparison of donating and nondonating families. Transplant Proc 2005;37:1557-9.
33. Kıraklı C, Uçar ZZ, Anıl AB, Özbek İ. The effect of shortening confirmed brain death diagnosis time on organ donation rates in the intensive care unit. J Crit Intensive Care 2011;1:8-11.

Medical Journal of Bakırköy

Med J Bakirkoy 2021;17:432-443
DOI: 10.4274/BMJ.galenos.2021.63496

Case Report

Intrahospital Transport of a Critically Ill Patient on Extracorporeal Membrane Oxygenation Support with Severe Acute Respiratory Distress Syndrome due to COVID-19

COVID-19'a Bağlı Ağır Akut Solunum Sıkıntısı Sendromlu Ekstrakorporeal Membran Oksijenasyon Desteğindeki Kritik Bir Hastanın Hastane İçi Transferi

Gülsüm Oya Hergünsel[1], Ayten Güreşçi Zeydan[1], Canan Kandemir[2], Berna Irmak Eser[2], Dilek Altun[3]

[1]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
[2]University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Nurse, Istanbul, Turkey
[3]Acıbadem Mehmet Ali Aydınlar University, Vocational School of Health Sciences, Department of Anesthesiology and Reanimation Istanbul, Turkey

ABSTRACT

Patients who do not respond to conventional mechanical ventilation (MV) support for respiratory failure due to the Coronavirus disease-19 may require the support of extracorporeal membrane oxygenation (ECMO). Intrahospital transportation of critically ill patients under MV and ECMO support carries potential risks that could be life-threatening. A structured process performed by a professional team plays a vital role in improving patient safety during transportation of the patient. In this presentation, we aim to share our experiences during the intrahospital transportation of a patient on ECMO support with appropriate equipment and a team of experienced personel.

Keywords: Extracorporeal membrane oxygenation, intrahospital transport, computed tomography scan, intensive care unit, Coronavirus disease-2019

ÖZ

Konvansiyonel mekanik ventilasyon (MV) desteğine yanıt vermeyen, Koronavirüs hastalığı-2019'a bağlı solunum yetmezliği olan hastalar, ekstrakorporeal membran oksijenasyonu (ECMO) desteğine ihtiyaç duyabilir. MV ve ECMO desteği altındaki kritik hastaların hastane içi nakli yaşamı tehdit eden birçok potansiyel riske sahiptir. Uygun ekipman ve deneyimli personelden oluşan bir ekip tarafından gerçekleştirilen yapılandırılmış bir süreç, hastanın nakli sırasında hasta güvenliğinin artırılmasında hayati bir rol oynar. Bu sunumda, ECMO desteğinde olan bir hastamızın hastane içi transportunda sırasındaki deneyimlerimizi paylaşmayı amaçladık.

Anahtar Kelimeler: Ekstrakorporeal membran oksijenasyonu, hastane içi nakil, bilgisayarlı tomografi taraması, yoğun bakım ünitesi, Koronavirüs hastalığı-2019

Address for Correspondence: Dilek Altun, Acıbadem Mehmet Ali Aydınlar University, Vocational School of Health Sciences, Department of Anesthesiology and Reanimation Istanbul, Turkey
Phone: +90 532 493 27 67 E-mail: drdilekaltun@gmail.com ORCID ID: orcid.org/0000-0003-2279-3083

Cite as: Hergünsel GO, Güreşçi Zeydan A, Kandemir C, Eser BI, Altun D. Intrahospital Transport of a Critically Ill Patient on Extracorporeal Membrane Oxygenation Support with Severe Acute Respiratory Distress Syndrome due to COVID-19. Med J Bakirkoy 2021;17:432-443

Received: 20.09.2021
Accepted: 11.10.2021

INTRODUCTION

Extracorporeal life support treatment like extracorporeal membrane oxygenation (ECMO) is recommended for the treatment of patients with severe acute respiratory distress syndrome (ARDS) and Coronavirus disease-2019 (COVID-19) (1).

ARDS, related to COVID-19, may be a life-threatening problem in patients if it is not treated early and effectively. Therefore, salvage treatments such as ECMO come to mind for patients with severe ARDS induced by the COVID-19. ECMO still has a major role and is recommended in the treatment of COVID-19 related ARDS in intensive care units (ICUs) (1,2).

Intrahospital transport of critically ill patients with ECMO support from ICU to hospital facilities such as imaging (radiology and cardiac catheterization) units and operating room has many potential risks, including respiratory compromise, hemodynamic instability, equipment failure, and hypothermia, and it needs effective teamwork (3).

In particular, critically ill patients followed-up in the ICU especially those with ECMO support, should be transported by an experienced multidisciplinary team with a minimum risk.

In this presentation, we aim to share our experience of transporting a patient with ECMO support after being attached with COVID-19 to the radiological imaging unit (3).

CASE REPORT

A 43-year-old male patient who had no previous disease was admitted to our emergency department with the complaints of fever and cough. On admission, his computed tomography scan showed an appearance of bilateral ground glass suggestive of viral pneumonia, and started on prophylactic medication having hydroxychloroquine sulfate, azithromycin, and oseltamivir for five days. The first polymerase chain reaction (PCR) test from nasopharangeal swab was confirmed to be positive for severe acute respiratory syndrome caused by Coronavirus-2. By the second day of the treatment, as his condition worsened, he was intubated and was shifted to our ICU. Following the initiation of COVID therapy, the patient was taken to the prone position intermittently under high settings of mechanical ventilation (MV). Despite of all the treatments, the patient could not keep the saturation at a sufficient level, and CO_2 retention continued to increase. Despite the implementation of all treatment strategies with a P/F ratio <100, they were not sufficient to prevent the progression of severe ARDS due to the viral pneumonia.

On the 15th day of hospitalization, due to severe hypoxia and severe metabolic and respiratory acidosis, veno-venous ECMO was planned for the patient. Continuous renal replacement therapy was started on the patient, who developed an acute renal failure. Due to hemodynamic instability, inotropic support was started. He was sedated with midazolam and fentanyl.

Since the ECMO treatment applied to the patient was insufficient in healing the lungs, lung transplantation was indicated, and he had to be transferred to the radiology unit-1 floor below the ICU for detailed radiological imaging. The transport of the patient to the radiological unit lasted for 40 minutes.

On the 22nd day his control, PCR test was negative. In addition, second and third control PCR tests were negative.

We planned to transfer the patient with ECMO support to the radiology unit.

The patient was taken to the radiology unit in his ICU unit bed. The hall monitorization continued during transport (preferable oxygen saturation, electrocardiography, invasive arterial pressure, central venous pressure).

According to the routine protocols of our clinic, some rules to be followed during patient transport have been introduced, and a transfer checklist has been developed in line with these rules. Transport was done by specialized staffs like a perfusionist (ECMO coordinator and also team leader for the transport), intensive care specialist, an anesthesiologist, perfusionist, two specialized intensive care nurse, and personnel. According to this, the patient transport form is filled by the intensive care specialist doctor and nurse, and the necessary information for the patient transport is collected before the patient is transported to the radiology unit. The intensive care specialist doctor and nurse, together, made sure that the transport monitor, patient bed, mechanical ventilator, and other equipment are ready for transport and fill in the necessary places in the transfer form. Transport ventilator settings are adjusted by the intensive care doctor, ensuring that the patient is safely connected to the transport ventilator. The fixed monitor of the patient was used for the transfer. There was no interruption in the patient's monitoring. It was ensured that the infusion systems were operational (Figure 1).

The transport procedure of the patient lasted for 40 minutes with no complications. The patient was carried to the ICU safely. After arriving at the ICU, the control blood gas sample was normal. The patient's hemodynamics remained stable throughout the transport. There were no complications in the transport process, in the radiology unit, and the ICU.

Figure 1. Monitorization of the patient during transport. Full monitoring has continued during transport

After transport, the patient was taken to the ICU in a stable condition.

The patient's written informed consent was obtained for the publication of the case report (clinical details and images) concerning his family.

DISCUSSION

Intrahospital transport of critically ill patients, especially with ECMO support has many potential risks (4). In this report, we aimed to evaluate the problems we experienced during the transport and the precautions taken to minimize these problems and improve quality/safety of the transport with the benefit of protocols carried out in our clinic to provide patients with the least error by the multidisciplinary professional staff. According to our experience, structured multidisciplinary handover process for transfer of patient was associated with improved information transfer, reduced postoperative complications and errors, more consistent and thorough information exchange, and improved compliance with the process measures (e.g., efficiency in equipment and monitoring line transfer) with provider satisfaction.

Intrahospital transport of patients with ECMO is crucial. If necessary precautions are not taken, it may lead to fatal complications. There are a lot of risks that may lead to serious and lethal complications during the transfer of critically ill patients on ECMO, including MV, ECMO support with cannulas placed in the main blood vessels, and multiple infusion pumps that require multiple long tubes (5-7).

Despite all the precautions taken by the experienced team, the transport of all critically ill patients is a very risky process. Publications are reporting that the complication rate may reach up to 70% if the necessary precautions are not taken (8). The fact that critical patients have multiple system dysfunction and minor physiological changes leads to serious morbidity, and mortality increases the importance of the process.

Hemodynamic deterioration is one of the most common problems (9,10). Since these patients mostly consist of the patient group receiving MV support, respiratory problems (protrusion of the intubation tube, non-ventilation of the patient, lack of aeration due to plugs caused by the secretions, etc.) come to the first (8-12). In these patients, the fact that hemodynamic support treatments are not interrupted, and the immediate elimination of the technical problems that occur in providing this is one of the most important factors in reducing the complications (9-12). During our transport, we did not see any hemodynamic instability.

Apart from these, technical and equipment problems may also be observed during transport. Preservation of surgical drains, instruments, and lines used in the drug infusion, and monitoring lines, which are important in patient follow-up, and early detection and prevention of related complications require a careful and experienced transport team. We transported our patient with a portable transport ventilator. Before transport, our intensive care specialist has checked the ventilator settings, arranged them, and got ready for the patient. Respiratory events can also be seen during the intrahospital transports (13).

The intrahospital transport of critically ill patients is a very risky process despite all the precautions taken by the experienced team (14). First, with the developing technological and medical opportunities, the life expectancy of the patients with the chronic diseases has increased, and the rate of operation has increased. ICUs cannot meet this need due to the patient group with a low bed capacity and a long hospital stay. In the retrospective review we conducted in our clinic, with the effective use of postoperative ICUs, the operations of this risky patient group are performed without further complications and delay, and the waiting time for the operation in the hospital will be reduced (11-15).

Structured multidisciplinary handover process for transfer of the patients was associated with an improvement in information transfer, reduction in postoperative complications, and errors.

Implementation of a structured handover process is associated with an improvement in information transfer, a decrease in specific complications (16).

ETHICS

Informed Consent: The patient's written informed consent was obtained for the publication of the case report (clinical details and images) concerning his family.

Authorship Contributions

Surgical and Medical Practices: G.O.H., D.A., Concept: G.O.H., A.G.Z., C.K., B.I.E., D.A., Design: G.O.H., A.G.Z., C.K., B.I.E., D.A., Data Collection or Processing: G.O.H., A.G.Z., D.A., Analysis or Interpretation: G.O.H., D.A., Literature Search: G.O.H., A.G.Z., D.A., Writing: A.G.Z., D.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. MacLaren G, Fisher D, Brodie D. Preparing for the Most Critically Ill Patients With COVID-19: The Potential Role of Extracorporeal Membrane Oxygenation. JAMA 2020;323:1245-6.
2. Shekar K, Badulak J, Peek G, Boeken U, Dalton HJ, Arora L, et al. Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: A Consensus Document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. ASAIO J 2020;66:707-21.
3. Extracorporeal Life Support Organization (ELSO) Guidelines for ECMO Transport Ann Arbor: ELSO. 2015. Available.
4. Prodhan P, Fiser RT, Cenac S, Bhutta AT, Fontenot E, Moss M, et al. Intrahospital transport of children on extracorporeal membrane oxygenation: indications, process, interventions, and effectiveness. Pediatr Crit Care Med 2010;11:227-33.
5. Venkategowda PM, Rao SM, Mutkule DP, Taggu AN. Unexpected events occurring during the intra-hospital transport of critically ill ICU patients. Indian J Crit Care Med 2014;18:354-7.
6. Warren J, Fromm RE Jr, Orr RA, Rotello LC, Horst HM; American College of Critical Care Medicine. Guidelines for the inter- and intrahospital transport of critically ill patients. Crit Care Med 2004;32:256-62.
7. Kue R, Brown P, Ness C, Scheulen J. Adverse clinical events during intrahospital transport by a specialized team: a preliminary report. Am J Crit Care 2011;20:153-61; quiz 162.
8. Nagpal K, Vats A, Ahmed K, Vincent C, Moorthy K. An evaluation of information transfer through the continuum of surgical care: a feasibility study. Ann Surg 2010;252:402-7.
9. Joy BF, Elliott E, Hardy C, Sullivan C, Backer CL, Kane JM. Standardized multidisciplinary protocol improves handover of cardiac surgery patients to the intensive care unit. Pediatr Crit Care Med 2011;12:304-8.
10. D'Empaire PP, Coburn N, Amaral AC. Frequency and quality of handover between the operating room and the intensive care unit. Am J Respir Crit Care Med 2012;185:A5079. Availabl form:https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2012.185.1_MeetingAbstracts.A5079
11. Kue R, Brown P, Ness C, Scheulen J. Adverse clinical events during intrahospital transport by a specialized team: a preliminary report. Am J Crit Care 2011;20:153-61; quiz 162.
12. Gleicher Y, Mosko JD, McGhee I. Improving cardiac operating room to intensive care unit handover using a standardised handover process. BMJ Open Qual 2017;6:e000076.
13. Hurst JM, Davis K Jr, Johnson DJ, Branson RD, Campbell RS, Branson PS. Cost and complications during in-hospital transport of critically ill patients: a prospective cohort study. J Trauma 1992;33:582-5.
14. Papson JP, Russell KL, Taylor DM. Unexpected events during the intrahospital transport of critically ill patients. Acad Emerg Med 2007;14:574-7.
15. Mazza BF, Amaral JL, Rosseti H, Carvalho RB, Senna AP, Guimarães HP, et al. Safety in intrahospital transportation: evaluation of respiratory and hemodynamic parameters. A prospective cohort study. Sao Paulo Med J 2008;126:319-22.
16. Salt O, Akpınar M, Sayhan MB, Örs FB, Durukan P, Baykan N, et al. Intrahospital critical patient transport from the emergency department. Arch Med Sci 2018;16:337-44.

2021 Hakem İndeksi - 2021 Referee Index

Abdil Cem İbiş
Abdullah Demirbaş
Afitap İçağasıoğlu
Ahmet Beşir
Ahmet Sebe
Ahmet Tan Cimilli
Ahmet Yozgat
Akın Çakır
Alev Kural
Ali Elitok
Ali Fuat Erdem
Ali Osman Gürol
Ali Özdemir
Aliye Çayır
Altug Duramaz
Amra Adrovic
Arif Yalçın
Arzu Gümüş
Asiye Gül
Aslı Sarandöl
Asuman Gedikbaşı
Ayfer Bakır
Aygen Türkmen
Aylin Yücel
Ayse Bahadır
Ayşe Batırel
Ayşe Burcu Erdoğdu
Ayse Fulya Maner
Ayse Kavak
Aysun Sıkar Aktürk
Bahadır Çiftçi
Bahar Beker
Barış Murat Ayvacı
Bilge Bayraktar
Bülent Durdu
Burak Açar
Burçe Can Kuzu
Çağlar Ödek
Çağrı Akalın
Çağrı Yayla
Can Sevinç
Ceren Can
Çiğdem Kekik Çınar
Cihan Kaya
Cihangir Akyol
Demet Bingöl
Didem Turgut Coşan
Dilek Altun
Elbis Ahbap
Elham Farzannejad
Elif Arı Bakır
Elif Gülsüm Ümit
Emre Baca
Eren Özçağlı
Eren Yıldızhan
Ersin Erçin
Esin Erdoğan
Eylem Ulaş Saz
Eyüp Gemici
Fatma Akyüz
Fatma Savran Oğuz
Fethi Gül
Feyza Nur Tuncer Kılınç
Figen Palabıyık
Fikret Çınar
Fulya Doğaner
Gökçen Garipoglu
Gökhan Cesur
Gökhan Umut
Gonca Bektaş
Gönenç Ortaköylü
Gül Karadağ
Güray Can
Güray Demir
Halil Dogan
Hasan Güngör
Hasan Koçoğlu
Hatice Polat
Hülya Güngel
Hüseyin Yüce Bircan
İbrahim Ali Özemir
İbrahim Ulaş Özturan
İlgin Özden
İlhan Yargıç
İlker Gül
Işıl Işık Andsoy
İsmail Cem Sormaz
İsmet Yalkın Çamurcu
Itır Şirinoğlu Demiriz
Jülide Ergil
Keziban Doğan
Kudret Keskin
Levent Dalar
M. Cevdet Avkan
Mehmet Ali Talmaç
Mehmet Bülbül
Mehmet Hurşitoğlu
Meltem Gürsu
Meltem Vural
Mensure Çakırgöz
Murat Duman
Murat Ekin
Murat Elli
Murat Kara
Mustafa Akkiprik
Mustafa Ümit Uğurlu
Naziye Ak
Nezih Ziroğlu
Nihan Çakır
Nihat Demirhan Demirkan
Nuri Alper Şahbaz
Oğuz Poyanlı
Oğuzhan Sunamak
Okcan Basat
Osman Şimşek
Oya Hergünsel
Özgen Işık
Özlem Bostan Gayret
Pınar Tarkun
Pınar Zeyneloğlu
Ramadan Özmanevra
Ramazan Sabırlı
Richard Pg Ten Broek
Ruşen Dündaröz
Sacide Pehlivan
Şahin Hamilçıkan
Sami Çifçi
Sema Alaçam
Semra Eroglu
Serap Argun Barış
Serdar Cömert
Serdar Hakan Başaran
Sevda Tanrıkulu Küçük
Seyit Ahmet Uçaktürk
Sezgin Sahin
Sibel Oba
Sinan Binboğa
Sinem Çakal
Süleyman Bayraktar
Süleyman Demiryas
Talip Karaçor
Tayfun Kara
Tolga Atakul
Tuba Bayındır
Tuğba Gürsoy Koca
Tuluhan Yunus Emre
Turgut Dönmez
Ufuk Erenberk
Vedat Erentuğ
Veysel Erden
Vildan Ertekin
Yasemin Çağ
Yasemin Coşkun Yavuz
Yavuz Demiraran
Yılda Arzu Aba
Zafer Çukurova
Zehra Eren
Zehra Kaya
Zeynep Çizmeci
Zeynep Karaali

2021 Yazar İndeksi - 2021 Author Index

2021 Yazar İndeksi - 2021 Author Index

2021 Yazar İndeksi - 2021 Author Index

2021 Konu İndeksi - 2021 Subject Index

2021 Konu İndeksi - 2021 Subject Index

2021 Konu İndeksi - 2021 Subject Index