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Fatih Şamil ULUDAĞ
(fsuludag@gmail.com)

CORRESPONDENCE ADDRESS

MediHealth Academy Publishing
Emniyet Mah., Yukarı Sk., 6/1, Yenimahalle, Ankara, Turkey
E-mail: info@medihealthacademy.com
Phone: +90 312 349 77 77

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EDITORIAL

Our dear readers,

We are proud to publish the first issue of our journal for 2022 with 60 articles. Day by day, we increase the scientific quality of our journal. We have followed by a wider audience over time. Principally, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as Scopus, PubMed and SCI-Expanded. I would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal. We hope that this issue will be useful to our readers.

Sincerely yours.

Assoc. Prof. Alpaslan TANOĞLU, MD.
Editor-in-Chief

CONTENTS

Original Article

CONTENTS

Original Article

CONTENTS

Original Article

CONTENTS

Original Article

CONTENTS

Original Article

Original Article

HEALTH SCIENCES
MEDICINE

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Acute postoperative pain and opioid consumption after laparoscopic cholecystectomy is associated with body mass index: a retrospective observational single-center study

Ökkeş Hakan Miniksar[1], Mehmet Kağan Katar[2]

[1]Yozgat Bozok University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Yozgat, Turkey
[2]Atlas University, Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

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ABSTRACT

Aim: The aim of this study was to determine the relationship between postoperative pain scores and opioid analgesic consumption according to BMI levels in patients undergoing laparoscopic cholecystectomy.

Material and Method: In this retrospective observational study, we scanned the medical data of 154 patients aged from 18-55 years who underwent laparoscopic cholecystectomy. Patients were divided into two groups based on the BMI cut-off value (Group Non-obese, BMI <30 kg/m², n=59; Group Obese, BMI >30 kg/m², n=35). Postoperative visual analog scale (VAS) pain scores, total tramadol consumption, and intraoperative fentanyl bolus requirements were compared between the groups at five-time points (T0: in the recovery room, T1: 1st hour in the ward, T2: 6th hour, T3: 12th hour, and T4: 24th hour).

Results: Postoperative VAS pain scores were significantly higher in the Group Obese at T1-2 time points (p=0.009). The number of patients with a VAS score of >3 at the T-0 time point was significantly higher in the Group Obese (p=0.014). Total tramadol consumption was significantly higher in the Group Obese (40.0±46.6 mg) than in the Group Non-obese (16.10±34.0 mg) (p=0.003). There was a weak positive correlation between BMI and postoperative pain scores (T0, T-1, T-2) of the patients, and a moderate positive correlation (r=0.307) between total tramadol consumption.

Conclusions: According to the results of this study, BMI is associated with acute postoperative pain in patients undergoing cholecystectomy, and obese patients require more opioid analgesia postoperatively. However, postoperative analgesia requirements should be determined according to BMI levels in patients undergoing cholecystectomy.

Keywords: Obesity, postoperative pain, analgesia, opioid consumption, laparoscopy

INTRODUCTION

Cholecystectomy is one of the most common intra-abdominal surgeries, usually performed laparoscopically. Although acute postoperative pain is less common in laparoscopic surgery compared to open surgery, many patients (30-70%) complain of moderate to severe pain (1).

Acute postoperative pain can be defined as pain that occurs due to a surgical procedure and decreases tissue healing over time. Many studies have reported an increase in length of stay, sleep disturbance, decrease in patient satisfaction, prolonged immobilization time and increase in opioid analgesic consumption due to poor control of postoperative pain (2). It may also cause the development of chronic pain (1-3). Therefore, it is important to treat it effectively (3).

Many factors such as the presence of preoperative pain, preoperative anxiety, applied analgesic treatment method, depression, surgical procedure, inflammation, neuronal damage, gender, smoking, obesity and age play a role in the etiology of postoperative pain (4). Therefore, it is difficult to fully assess postoperative pain and apply a standard treatment. Although the cause of postoperative pain is inflammation and neuronal damage, its pathophysiology is typical and outcomes vary according to the patient. For this reason, it is necessary to obtain new information on pain mechanisms to identify patients at high risk of postoperative pain in the preoperative period and to develop individual treatment strategies (1-4).

Corresponding Author: Ökkeş Hakan Miniksar, hminiksar@yahoo.com
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The relationship between overweight and pain has been the subject of many studies. A high body mass index (BMI) has been associated with many types of pain, such as general body pain, back pain, and migraine (5). In a comprehensive study, it was reported that higher BMI was predictive of poor postoperative pain control (6). Conversely, in another study, it was reported that there was no relationship between BMI and pain (7). However, the relationship between body mass index and postoperative pain is still controversial. Therefore, the potential relationship between overweight or obesity and postoperative pain needs to be investigated by further clinical studies. In addition, determining the relationship between preoperative BMI levels and postoperative acute pain scores and opioid consumption in patients who will undergo laparoscopic cholecystectomy (LC) surgery may help clinicians' pain management strategies.

We hypothesized that BMI correlated with postoperative pain scores and opioid analgesic consumption. Therefore, the main aim of this study was to evaluate postoperative pain scores and opioid analgesic consumption, according to BMI levels in patients who underwent LC. The secondary aim was to determine the correlation of BMI levels with postoperative pain scores and opioid analgesic consumption.

MATERIAL AND METHOD

Study Design

This retrospective observational single-center study was conducted out at Yozgat Bozok University Medical Faculty Hospital, a tertiary medical center. The study was approved by the Yozgat Bozok University Clinical Researchs Ethics Committee (Date: 27.01.2021, Decision No: KAEK-189_2021.01.27_05) and the Helsinki Declaration guidelines were followed throughout the study. The requirement for written informed consent was waived.

Study Participants

In this study, 154 adult patients of American Society of Anesthesiologist (ASA) physical status 1-3 and over 18 years of age who underwent elective LC between May 2018 and July 2020 were examined. Demographic characteristics of patients, ASA physical status, duration of operation, BMI, and other data were obtained retrospectively from evaluation forms recorded in the anesthesia polyclinic during the preoperative period, anesthesia follow-up forms, patient files, and the hospital information management system. Patients receiving known pain treatment, pregnancy, patients with ASA-IV, undergoing another invasive procedure in addition to LC, patients with an additional neurological and psychiatric history, intraoperative conversion to open cholecystectomy, emergency cases, intraoperative and postoperative non-protocol analgesic applied and records (intraoperative, PACU or ward) missing were excluded from the study. A total of 94 patients remained included in the study (**Figure 1**).

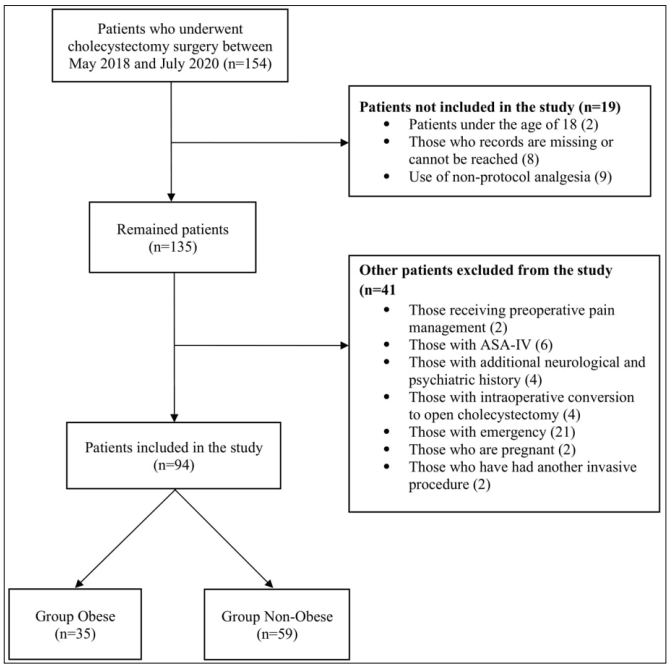

Figure 1. Flow diagram of the study

Clinical Data

Patients were classified according to their BMI scores as Group Obese (BMI>30 kg/m²) and Group Non-Obese (BMI<30 kg/m²). During the operation, standard institutional anesthetic induction, monitoring, and maintenance protocol were followed in the study. All patients received standardized anesthesia induction (2-3 mg/kg propofol, 0.6-1.2 mg/kg rocuronium and 1 µg/kg fentanyl). After orotracheal intubation, patients were set to maintain a tidal volume of 8 mL/kg, I: E ratio 1:2, respiratory rate 12/min, $ETCO_2$ 30 to 40 mmHg in controlled ventilation mode. Maintenance of anesthesia was provided by inhalation of 60% O_2 and 40% air and sevoflurane (minimum alveolar concentration [MAC] 0.8-1.3). All surgeries were performed by experienced general surgeons. All patients were given 1 mg/kg tramadol IV and 1 g paracetamol IV for postoperative analgesia, according to the pain protocol of our institution, approximately 30 minutes before the end of the operation. At the end of the surgery, residual neuromuscular blockade was antagonized with neostigmine and atropine. When the patient was awake, the endotracheal tube was extubated and the patients were transported to the recovery room. For postoperative pain management, all patients were administered three times a day IV dexketoprofen trometamol 50 mg as a standard. If sufficient analgesia was not provided, in the first step, tramadol 50 mg iv was administered. The total tramadol consumption of patients in the postoperative first 24 hours was recorded.

The additional dose of fentanyl administered to the patients intraoperatively, the VAS (visual analog scale) (0–10) pain scores in the postoperative recovery unit, the number of patients with VAS >3/10, and the presence of nausea and vomiting were recorded according to the anesthesia follow-up form. In the first 24 hours postoperatively, the follow-up parameters were recorded by examining the nurse observation form. The data were analyzed retrospectively at five-time points in the postoperative period: T0: recovery room, T1: 1st hour in the ward, T2: 6th hour in the ward, T3: 12th hour in the ward, and T4: 24th hour in the ward (**Figure 2**). VAS resting pain scores (0 = no pain and 10 = worst possible pain), additional opioid analgesic amounts, and presence of nausea-vomiting at all postoperative time points (T0-T4) of the patients were recorded by examining the patient follow-up forms. All these variables were compared between obesity groups.

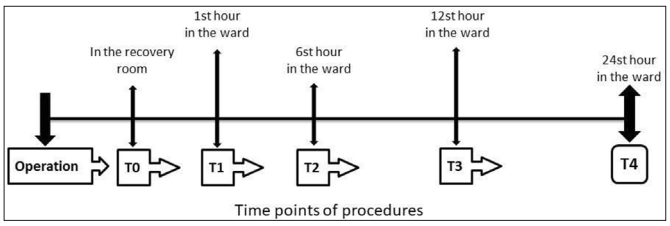

Figure 2. Time points of procedures

RESULTS

Analysis of Clinical Variables by Obesity Groups

Postoperative VAS pain scores were higher in the obese group at T1-2 time points and showed a significant difference (p= 0.009) (**Table 1**). There was no statistically significant difference between the groups at other time points (p>0.05). The number of patients with a VAS score of >3 at the T-0 time point was significantly higher in the obese group (p=0.014). 19 (54.3%) patients in the obese group and 17 (28.8%) patients in the non-obese group required additional boluses of fentanyl intraoperatively (p=0.039). Total tramadol consumption was found to be 16.10±34.0 significantly higher in the obese group than in the 40.0±46.6 non-obese group (p=0.003) (**Table 2**). The nausea was observed in 9 (25.7%) patients in the obese group and 6 (10.2%) patients in the non-obese group (p=0.047). Vomiting was observed in 5.3% (5/94) of the patients. There was no significant difference between the groups in terms of postoperative vomiting.

Correlation Analysis of BMI and Clinical Variables

There was a weak positive correlation between BMI and postoperative pain scores (T0, T-1, T-2) of the patients, and a moderate positive correlation (r=0.307) with total tramadol consumption (**Table 3**).

Table 1. Demographic data by obesity groups

	Group Non-obese (n = 59)	Group Obese (n = 35)	Total (n =94)	P value
Age (years)	37.5 ± 4.0	38.9 ± 3.8	38.1 ± 3.9	0.105[a]
Gender, n (%)				0.142[b]
Male	24 (40.7)	9 (25.7)	33 (35.1)	
Female	35 (59.3)	26 (74.3)	61 (64.9)	
ASA physical state, I/II/III (%)	25/29/5 (42.4/49.2/8.5)	10/20/5 (28.6/57.1/14.3)	35/49/10 (37.2/57.1/10.6)	0.352[b]
Weight (kg)	66.8 ± 7.7	90.4 ± 13.3	75.6 ± 15.2	**<0.001[a]**
Height (m)	1.8 ± 0.8	1.6 ± 0.1	1.7 ± 0.1	**0.001[a]**
BMI (kg/m²)	25.9 ± 1.7	36.4 ± 2.6	29.8 ± 5.5	**<0.001[a]**
Operation time (minutes)	72.1 ± 10.4	71 ± 12.7	71.7 ± 11.3	0.631[a]

ASA: American Society of Anesthesiologist. BMI: Body Mass Index. Data are presented as the mean ± SD for continuous variables and number and percentage for categorical variable. aCompared by independent sample t-test. bCompared by Pearson's chi-square test. P values in bold text indicate statistical significance at P < 0.05.

Table 2. Clinical characteristics according to obesity groups

	Group Non-obese (n = 59)	Group Obese (n = 35)	Total (n =94)	P value
VAS score > 3 patients, n (%)				**0.014[a]**
No	42 (71.2)	16 (45.7)	58 (61.7)	
Yes	17 (28.8)	19 (54.3)	36 (38.3)	
Pain VAS score-T0	3 [2 to 4]	4 [3 to 5]	3 [3 to 5]	**0.026[c]**
Pain VAS score-T1	2 [2 to 3]	2 [2 to 3]	2 [2 to 3]	**0.009[c]**
Pain VAS score-T2	2 [1 to 2]	2 [2 to 2]	2 [1 to 2]	**0.009[c]**
Pain VAS score-T3	2 [1 to 2]	2 [2 to 2]	2 [1 to 2]	0.139[c]
Pain VAS score-T4	2 [1 to 2]	2 [2 to 3]	2 [1 to 2]	0.068[c]
Patients requiring fentanyl bolus intraoperatively, (%)	33 (55.9)	27 (77.1)	60 (63.8)	**0.039[a]**
Total tramadol consumption	16.10 (34.0)	40.0 (46.6)	25 (40.6)	**0.003[b]**
Nausea				**0.047[a]**
No	53 (89.8)	26 (74.3)	79 (84.0)	
Yes	6 (10.2)	9 (25.7)	15 (16.0)	
Vomiting				0.062[a]
No	58 (98.3)	31 (88.6)	89 (94.7)	
Yes	1 (1.7)	4 (11.4)	5 (5.3)	

Data are presented as the mean ± SD, median [interquartile range] for continuous variables and number and percentage for categorical variable. aCompared by Pearson's chi-square test. bCompared by independent sample t-test. cCompared by Mann-Whitney U test. Pain scores reported on a VAS (Visual Analog Scale) ranging from 0 to 10.

Table 3. Correlation analysis between BMI, postoperatıve pain scores and total tramadol consumption

	BMI	1	2	3	4	5
1. VAS-T0	.207*	1				
2. VAS-T1	.287**	.749**	1			
3. VAS-T2	.206*	.538**	.660**	1		
4. VAS-T3	.171	.379**	.480**	.740**	1	
5. VAS-T4	.134	.381**	.492**	.595**	.735**	1
6. Total tramadol consumption	.307**	.487**	.476**	.448**	.257*	.370**

*Correlation is significant at the .05 level (2-tailed). **Correlation is significant at the .01 level (2-tailed). VAS, Visual Analog Scale; BMI: Body Mass Index

DISCUSSION

The aim of this retrospective study was to investigate the relationship between BMI and postoperative pain scores and analgesic consumption in patients who underwent LC. Several important findings were identified in the present study. First; postoperative pain scores were higher in obese patients. Second; intraoperative opioid requirement and total opioid consumption were higher in obese patients. Finally; a significant correlation was found between BMI scores and postoperative pain scores and opioid consumption.

Acute postoperative pain is defined as pain of rapid onset and short duration resulting from nociceptive stimulation of tissues induced by operative stress. Pain sensitivity is highest during the first 24 hours postoperatively and gradually decreases over this period (8). Despite increasing knowledge and experience in the treatment of acute postoperative pain, acute pain after laparoscopic surgery is still a major problem (5). It is known that the incidence of postoperative pain after laparoscopic surgery can be up to 70%. In our study, in accordance with the literature, approximately 38.3% of the patients in the postoperative recovery unit had VAS pain scores >3.

Many previous studies have examined the relationship between BMI and various pain syndromes (6,9). These studies have shown that high BMI is a risk factor for perceived pain (6). In a meta-analysis in which 53,362 patients were examined and 33 studies were included, it was revealed that higher BMI may be a predictor of poorly controlled acute postoperative pain (6). In the same study, young age, female gender, smoking, history of depressive symptoms, history of anxiety symptoms, sleep difficulties, and use of preoperative analgesia were also reported as other risk factors (6). In our study, the number of patients with VAS >3 at the T-0 time point was found to be higher in the obese group. However, pain scores were higher in the obese group during the first 12 hours. In addition, in the study of Elgendy et al. (10), the analgesic requirements of morbidly obese and super-morbid patients who underwent laparoscopic sleeve gastrectomy were compared. In this study, recovery unit tramadol consumption and total paracetamol consumption showed significant differences between the groups. Moreover, postoperative pain scores and hemodynamic stability values were similar between the groups. In another past study, in ambulatory surgery patients; BMI, duration of anesthesia, and certain types of surgery were found to be important determinants of pain in the post-anesthesia care unit (11). Based on these results, high BMI may also be a risk factor for the presence of postoperative pain in LC patients. These evidences in the literature strengthen our hypothesis that there is a relationship between postoperative pain and BMI levels.

When the literature is examined in detail, there are also studies reporting that BMI is not associated with postoperative pain and opioid consumption (7,12). Cristina et al. analyzed the relationship of BMI and some serum tissue damage markers with postoperative pain in a study they conducted in patients undergoing inguinal hernia surgery. In this study, contrary to what is known, the authors reported that higher BMI is not associated with higher postoperative pain and that high serum LDH levels can provide useful information to predict moderate to severe postoperative pain (12). Similarly, Grodofsky et al. (7) in a study conducted in patients undergoing ankle fracture surgery, aimed to determine the relationship between gender and BMI and acute postoperative pain scores. In this study, patients received only morphine as preemptive analgesia, and no association was found between obesity or gender and postoperative pain (7).

Although the physiological mechanism of the relationship between obesity and pain has not yet been clearly explained, various hypotheses have been put forward. When the studies are examined in detail, there are limited studies in this field and the evidence is insufficient. In the literature, obesity-related pain has been studied from three aspects: mechanical (mechanical pressure on tissue and joint), behavioral (sleep and physical activity), and physiological (inflammatory theory) (13,14). It has been reported that obesity is basically a low-grade inflammatory disease and obesity-related pain is associated with a systemic inflammatory state. It has been reported that modulators such as proinflammatory cytokines (TNF-α, IL-6, IL-1β, and leptin), ghrelin, and galanin cause an increase in pain sensitivity in patients with obesity (13-16). All these mechanisms in the literature show that BMI is associated with various types of pain.

Another result of this study was that patients who needed intraoperative fentanyl were more common in the obese group. Our results are consistent with studies in the literature revealing the relationship between BMI and pain (6,9,13-16). Unlike our study, Elgendy et al. found that intraoperative fentanyl and morphine consumption was lower in super morbidly obese patients. As the reason

for this result; reported that since obese patients are more sensitive to opioids, the application of effective multimodal analgesia in their institute may contribute to reducing the intraoperative or postoperative opioid requirements (10). Pain regulation has been associated with endogenous opioids in the literature. However, in an experimental study, it was reported that basal endogenous opioid levels were higher in obese mice (17). On the other hand, Elderly et al. also claimed in their study that less need for analgesia in super-obese patients may be due to higher endogenous endorphin levels in obese patients (10).

Management of postoperative pain in obese patients is specific. Postoperative pain management should be multimodal to provide effective postoperative analgesia, facilitate physiotherapy and mobilization, and avoid opioid-related side effects. Paracetamol can be used safely for this purpose, but its effectiveness is limited (18). In our study, it was determined that the patients routinely received IV paracetamol twice a day according to the clinical protocol. Despite this treatment protocol, it was observed that especially obese patients consumed more opioids. NSAIDs are recommended for multimodal analgesia because of better analgesia, reduced opioid consumption, and fewer side effects (18).

One of the results of our study; obese patients have a higher incidence of nausea. These results are consistent with previous published studies. Nausea-vomiting is an important problem frequently encountered in the acute postoperative period. The causes of this problem may be due primarily to obesity or the high doses of opioids used more in obese patients. It is known that side effects of opioids such as nausea and vomiting are common (19,20). It has been reported in the literature that increased BMI is an important risk factor for postoperative nausea and vomiting (19). Conversely, there is also a study reporting that increased BMI is not a risk factor for postoperative nausea and vomiting (20).

This study has some limitations. Retrospective design, single-center design, small study population, short postoperative follow-up, and reliance on subjective pain scores are some of the limitations of this study.

CONCLUSION

According to our conclusion from this study, BMI is associated with acute postoperative pain and obese patients need more postoperative opioid analgesia. For this reason, it is necessary to determine the need for analgesia in patients who will undergo laparoscopic cholecystectomy in the acute postoperative period, after taking into account the obesity status. Our results should be supported by multicenter, randomized, and large patient series.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Yozgat Bozok University Clinical Researchs Ethics Committee (Date: 27.01.2021, Decision No: KAEK-189_2021.01.27_05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

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Temporal change of ventricular repolarization indices and index of cardioelectrophysiological balance (iCEB) during COVID-19 treatment including hydroxychloroquine at a tertiary referral hospital

Çaşıt Olgun Çelik[1], Orçun Çiftci[2], Gaye Ulubay[3], İbrahim Haldun Müderrisoğlu[2]

[1]Başkent University, Konya Practise and Research Hospital, Department of Cardiology, Konya, Turkey
[2]Başkent University, Ankara Training and Research Hospital, Department of Cardiology, Ankara, Turkey
[3]Başkent University, Ankara Training and Research Hospital, Department of Pulmonary Disease, Ankara, Turkey

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ABSTRACT

Aim: Hydroxychloroquine (HCQ) is widely administered to patients with confirmed or suspected COVID-19. It may increase the risk of cardiac arrhythmias associated with QT and QTc prolongation. This study aimed to assess the change in iCEB, a new marker of drug-induced arrhythmia, and other repolarization parameters in suspected COVID-19 patients treated with short-course HCQ.

Material and Method: This was a retrospective cross-sectional study including 40 patients hospitalized with suspected COVID-19 according to the CT findings and treated with HCQ. Serial assessments of the QT and QTc intervals and the calculation of the index of cardio-electrophysiological balance (iCEB) were performed using standard 12 lead electrocardiogram before hydroxychloroquine treatment, on the second day of HCQ treatment, and after the day of the last administered dose.

Results: QT, QTcB, QTcF, iCEB, iCEBcB significantly increased on the second day of HCQ treatment compared to baseline (p=0.009, p=0.001, p=0.002, p=0.047, p=0.05, respectively). Similarly, QT, QTcB, QTcF, iCEBcB and iCEBcF were significantly higher on the fifth day compared to baseline (p=0.011, p=0.005, p=0.005, p=0.013, p=0.028, p=0.024 respectively). However, there were no differences between the second and the fifth days of treatment for any of the studied parameters.

Conclusions: QT, QTc, and iCEB significantly increased compared to baseline on the second day, and remained increased on the fifth day of treatment. The differences were attributed to the amount of loading dose and the duration of HCQ treatment. Our study suggests that, along with other ECG markers, iCEB can be used in COVID-19 patients treated with HCQ.

Keywords: Hydroxychloroquine, COVID-19, QTc, iCEB, repolarization

INTRODUCTION

The new type of Coronavirus (SARS-Cov-2) has spread from China to the whole world and caused a pandemic that has caused serious medical, social, and economic problems worldwide. The disease termed as COVID-19 infection caused by the SARS-Cov-2 virus results in a wide range of clinical presentations ranging from asymptomatic course to mild flu-like clinics to severe pneumonia and hyperinflammatory response, with the latter potentially requiring intensive care and even causing death. In the case of serious disease, COVID-19 is a systemic disease with hyperinflammation, cytokine storm, and elevated cardiac enzymes (1). The risk classification for sudden cardiac death is still challenging due to drug-induced arrhythmias, acquired heart disease, or congenital heart disease. There are a few but commonly used risk markers to determine the risk of sudden cardiac death in patients with drug-induced arrhythmias. The QT interval is an ECG parameter reflecting action potential duration and one of the most widely used ECG risk markers for arrhythmias (2). Prolonged QT and QTc intervals are used as a common risk marker for torsades de pointes (TdP), polymorphic ventricular tachycardia (VT), and ventricular fibrillation (VF). However, additional biomarkers are needed for the patients who are at risk for the development of non-TdP-induced

Corresponding Author: Çaşıt Olgun Çelik, drolgunclk09@gmail.com
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VT/VF since the risk can not be identified only by evaluating QT or QTc. It is known that although some drugs prolonging the QT interval are proarrhythmic, the absence of QT prolongation does not mean freedom of arrhythmia risk. Therefore, there is a need for identifying better risk markers for drug-induced arrhythmias (3). Index of cardio-electrophysiological balance (iCEB), a new non-invasive ECG marker, compares the balance of depolarization and repolarization duration of the myocardial action potential and has been recently identified as a potential risk marker for drug-induced arrhythmia in an animal-based experimental study (4). Defined as a new marker for drug-induced arrhythmias, iCEB is calculated by dividing the QT interval by the QRS duration. It is assumed that iCEB is equivalent to cardiac wavelength λ (λ = effective refractory period (ERP) x conduction velocity), with an increased or decreased iCEB value would potentially predict increased sensitivity to TdP or non-TdP-mediated VT/VF (5). In a previous study in humans, iCEB was found lower in patients with Brugada syndrome and those who were administered arrhythmogenic drugs. It was stated that iCEB was a useful tool to detect an increased risk of both TdP and non-TdP-mediated VT/VF; hence, iCEB can arguably be a universal marker for ventricular arrhythmias (6).

In patients with COVID-19, blood pressure abnormalities and different arrhythmias such as tachycardia, bradycardia, or asystole are observed at a higher rate in critically ill patients (7,8). Arrhythmias in this population can occur secondary to hypoxemia, metabolic disorders, systemic inflammation, or myocarditis. In some publications published during the COVID-19 pandemic, it has been stated that treatment with hydroxychloroquine (HCQ) and/or azithromycin caused prolonged QT and QTc, at times resulting in TdP. However, it has been recently stated that the concomitant use of high dose HCQ with azithromycin rather than the standalone use of either agent in COVID-19 leads to QT and QTc prolongation and may result in TdP (9-11). Although it is suggested that the main cause of TdP in COVID-19 patients treated with HCQ is the combination of COVID-19's cardiac involvement, coexisting conditions such as severe kidney disease, older age, severe liver disease, and high dose HCQ and/or azithromycin use, it is still unclear whether ventricular arrhythmias occur due to the critical QT prolongation by HCQ independently of the COVID-19 disease (9). Although the benefit of HCQ in COVID-19 is controversial, it is still used as a treatment option in some countries including Turkey. In this paper, we aimed to investigate the temporal changes in ventricular repolarization indices and iCEB in patients with suspected COVID-19 treated with short-term HCQ.

MATERIAL AND METHOD

This study was approved by Başkent University Non-Interventional Clinical Research Ethics Committee (Date: 2021, Project No: KA20/227, Decision No: 21/127). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between April 2020-July 2020, we retrospectively reviewed the medical records of 116 patients with suspected COVID-19, of whom we enrolled 38 eligible patients. The patients with electrolyte abnormalities, chronic inflammatory disease, moderate to end-stage renal disease (GFR<30 ml/min), bundle branch block, atrial fibrillation, preexcitation syndromes, or use of any drug affecting QT duration were excluded. The patients treated with HCQ and other antibiotic regimens such as azithromycin were also excluded. The inclusion criterion was having typical COVID-19 symptoms combined with pulmonary ground-glass opacities on thoracic computed tomography (CT). All patients received HCQ treatment for 5 days according to our hospital treatment policy protocol for COVID-19. All patients' PCR results taken at the time of hospitalization and in the follow-ups were negative. Even though the patients had PCR negative test results, they were still treated with HCQ due to the clinical and CT findings during their hospitalization and discharged after having two consecutive negative PCR tests. On the first day, the patients were administered 400 mg PO HCQ twice a day followed by 200 mg PO HCQ twice a day for at least 4 days. HCQ was stopped after the fifth day of the treatment. The patients' demographic and clinical characteristics, as well as baseline laboratory findings (serum creatinine, potassium, magnesium, white blood cell count, platelet count, neutrophil/lymphocyte ratio, CRP, and troponın I), were recorded on admission. A 12-lead surface electrocardiogram (ECGs) was obtained from each patient using GE Healthcare MAC 2000 (General Electric, Milwaukee, USA) ECG recorder with a paper speed of 25 mm/s and voltage of 10 mm/mV. The ECGs were taken before the start of HCQ treatment on the second day of HCQ treatment (which corresponded to after 800 mg loading dose of HCQ and after the last dose of HCQ regimen. Electrocardiographic parameters including heart rate, QRS duration, and QT, interval were measured manually. All ECG measurements were calculated and analyzed by the same cardiologist. QTc interval was calculated manually by using Bazett's and Fridericia's formulas. Index of Cardio-Electrophysiological Balance (iCEB) was calculated manually by dividing the QT interval by the QRS duration. We also calculated corrected iCEB durations (iCEBcB and iCEBcF), by

dividing the QTc interval calculated by using Bazett's and Fridericia's formulas, respectively, by the QRS duration. Prolonged QTc was defined as ≥450 ms for adult males and ≥460 ms for adult females; based on the literature data, the QTc cut-off value for an increased TdP risk was accepted as 500 ms.

Statistical Analysis

IBM SPSS Statistics volume 25.0 (SPSS Inc, IBM, USA) was used for the statistical analyses. Descriptive statistics included median (interquartile range, min-max (IQR)) for non-parametric quantitative variables and number and percentage for categorical variables. Quantitative variables were tested for normality of distribution using the Shapiro-Wilk test. The Friedman test was used to make the paired comparison of the ECG parameters of the patients at three different times. A p-value of less than 0.05 was considered statistically significant.

RESULTS

This study included 40 eligible patients who were hospitalized with suspected COVID-19 and received a short course of HCQ regimen. Two patients died at the hospital due to non-arrhythmic causes (one from myocardial infarction and the other from hospital infection) after the start of the HCQ treatment. Of the 40 patients, 24 were male (60%) and 16 were female (40%). The median age was 61.5 (Interquartile range (IQR) 39-89) years. Their demographic data and clinical characteristics are given in **Table 1**. The comparison of ECG parameters between baseline and the second day of HCQ treatment, between the second day and after the fifth day of HCQ treatment, and between baseline and after the fifth day of HCQ treatment are given in **Table 2**. The proportions of patients with prolonged baseline QTcB, second-day QTcB, fifth-day QTcB and prolonged baseline QTcF, second-day QTcF, fifth-day QTcF values were 13.1% (n=5, 3 male and 2 female patient), 36.8% (n=14, 8 male and 6 female patients) 36.8% (n=14, 10 male and 4 female patients) and 2.6% (n=1, one male patient), 5.2% (n=2, 2 male patients) and 15.8% (n=6, 4 male and 2 female patients) respectively. Besides, the temporal changes of QT, QTcB, QTcF, iCEB, iCEBcB and iCEBcF are shown in **Figure 1**. When the baseline and the second day ECG parameters were compared QT interval, QTcB, QTcF, iCEB, iCEBcB were significantly greater on the second day than the baseline values (p=0.009, p=0.001, p=0.002, p=0.047, p=0.05, respectively); there was a trend for statistical significance for iCEBcF between the second day and baseline values (p=0.056). There was no significant difference between heart rate and QRS duration of baseline and the second day (p=0.361 and p=0.659). QT, QTcB, QTcF, iCEBcB, and iCEBcF were significantly greater on the fifth day compared to baseline (p=0.011, p=0.005, p=0.005, p=0.013, p=0.028, p=0.024, respectively). However, there was no significant difference between QRS duration and heart rate values of the fifth day and baseline (p=0.361 and p=0.659). Finally, no significant difference was observed between the second day and the 5th day concerning any of the ECG parameters (p=0.824 for QT, p=0.876 for QTcB, p=0.719 for QTcF, p=0.235, p=0.296 for iCEB, p=0.401 for iCEBcB, p=0.300 for iCEBcF, p=0.887 for QRS).

Table 1. Demographic and clinical characteristics of the patients treated with HCQ

Variable	Patients treated with hydroxychloroquine
Age (years)	61 (39-89)
Sex (male)	24 (60%)
Smoking	12 (31.5%)
Hypertension	17 (44%)
Diabetes mellitus	6 (15.7%)
Coronary atherosclerotic disease	8 (21%)
Ischemic cerebrovascular disease	4 (10.5%)
Pulmonary disease	6 (15.7%)
Creatinine (mg/dL)	0.84 (0.54-2.15)
K (mmol/L)	4.2 (3.5-4.7)
Mg (mg/dL)	2.04 (1.8-2.4)
WBC (10^3/μL)	7.62 (3.7-16.45)
Lymphocyte (10^3/μL)	1.62 (0.15-6.12)
Platelet (K/μL)	248 (58-390)
Neutrophil/lymphocyte ratio	3.32 (0.71-23.4)
CRP (mg/L)	56.9 (0.5-254.5)
Troponin (ng/mL)	0.005 (0-7.085)
Diuretics use	6 (15.7%)
Hospitality (days)	6 (5-30)
CT findings	40 (100%)
Unilateral ground-glass opacity	26 (63.1%)
Bilateral ground-glass opacity	14 (36.9%)

Table 2. Comparison of the baseline, second day, and fifth day ECG parameters of the suspected COVID-19 patients treated with HCQ

Variable	Baseline (IQR)	2nd day (IQR)	5th day (IQR)
QT (msec)	365.57 (69)	386.5 (66)*	381 (54)**
QTcB (msec)	425.5 (28)	441.5 (45)#	442 (42)##
QTcF (msec)	406.5 (31.75)	420 (40.5)†	417 (24)††
iCEB	3.95 (0.94)	4.11 (1.04)‡	4.26 (1.17)‡‡
iCEBcB	4.50 (1.23)	4.58 (1.02)§	4.83 (1.17)§§
iCEBcF	4.23 (1.14)	4.36 (1.05)Ψ	4.62 (0.99)ΨΨ
Heart rate (/min)	84.5 (31)	82 (19)	80.5 (23)
QRS (msec)	91 (20)	93.5 (18)	91.5 (18)

*= P=0.009 versus baseline, **= P=0.011 versus baseline, #= P=0.001 versus baseline, ##= P=0.005 versus baseline, †= P=0.002 versus baseline, ††= P=0.005 versus baselinei, ‡= P=0.047 versus baseline, ‡‡=P=0.017 versus baseline, §= P=0.050 versus baseline, §§= P=0.028 versus baseline, Ψ= P= 0.056 versus baseline,ΨΨ= P= 0.024 versus baseline

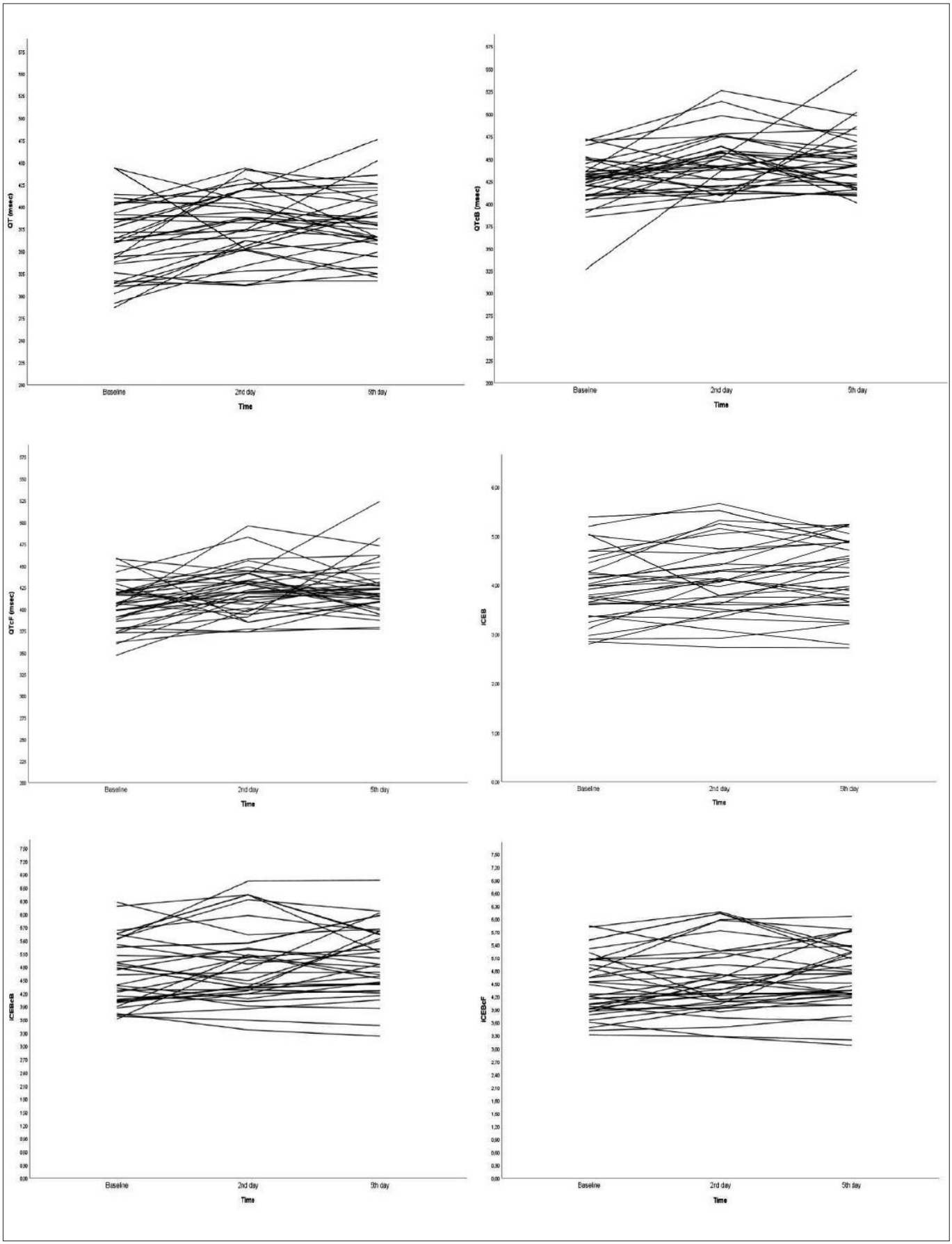

Figure 1. Multilinear graphical representation of the change of baseline, second day, and fifth-day values of ECG parameters of each patient. When the 2nd day values were compared with the baseline values, a statistically significant increase was observed for QT, QTc, iCEB, iCEBcB. However, there was an insignificant increase when 2nd day iCEBcF compared to the baseline values (p=0.056). QT, QTcB, QTcF, iCEBcB, and iCEBcF were significantly greater on the fifth day compared to baseline. When compared the second day and the 5th day values of QT, QTc, iCEB, iCEBcB, and iCEBcF, there was no significant difference between them.

DISCUSSION

COVID-19 infection, which may present as a novel microvascular thrombo-inflammatory syndrome leading to multiorgan failure and death. During the first wave of the epidemic, the disease has been treated intensively using certain drugs such as hydroxychloroquine (HCQ) and azithromycin, both of which portend a risk of QTc interval prolongation and ventricular arrhythmias. Clinically, acute myocardial damage, arrhythmias, and cardiogenic shock have been observed in the disease course in addition to the major respiratory manifestations of COVID-19. COVID-19 may also cause ECG abnormalities such as wide QRS complexes (>120 ms), prolonged QTc interval, lateral ST-T segment abnormalities, abnormal PR intervals with increased heart rate, and cardiac arrhythmias (12,13). A prolonged QTc interval has also been particularly reported in a variety of studies in COVID-19 as the predominant side effects of hydroxychloroquine/chloroquine and azithromycin (9). Although the use of HCQ with other antibiotics has been shown to prolong QTc, to affect ventricular depolarization, and, rarely, to cause TdP, only a few studies are examining the effect of isolated HCQ use in COVID-19 treatment on ventricular repolarization parameters in the literature; even more notably, no studies have ever investigated the effect of HCQ on iCEB (14,15). Thus, the present study aimed to investigate the changes of iCEB along with other ventricular repolarization parameters in patients treated with the HCQ alone. It found that after using high dose HCQ (800 mg/day), QT, QTcB, iCEB, iCEBcB, and iCEBcF significantly increased after the HCQ treatment compared to the baseline values. Although QTc calculated by Fridericia's formula is more accurate than that calculated by Bazett's formula, there was a non-significant difference between the baseline and 2nd-day iCEBcF values. The finding that there were only significant differences between the baseline values of iCEB, iCEBcB, QT, QTcB, and QTcF and the 2nd-day and 5th-day values may be explained that the increases in QT, QTc, iCEB, iCEBcB, and iCEBcF may have been linked to the higher loading doses of HCQ. However, we did not observe any TdP or other fatal ventricular arrhythmias during the hospitalization of the patients, and only two patients died from secondary problems (one died from myocardial infarction and the other one from hospital infection) after the start of the HCQ treatment. We could not make any comparison between the deceased patients and the survivors regarding the repolarization parameters due to the low number of the former. However, iCEB remarkably increased after HCQ use and we still believe that it may be a useful novel marker of ventricular repolarization and ventricular arrhythmias apart from QT/QTc, particularly after high doses of HCQ.

In recent studies, adverse events were found more frequent in HCQ-treated patients than in non-HCQ-treated ones (16,17). Recently there has been a plethora of retrospective and prospective studies about HCQ's effect on QT and QTc intervals and the risk of ventricular arrhythmias. Some of these studies have pointed that HCQ had no significant effect on QT and QTc intervals and no effect on the occurrence of ventricular arrhythmias while some others have reported significant QT and QTc prolongation but the rare occurrence of fatal ventricular arrhythmias or death (12-15,17-19). It has been argued that, besides QTc prolongation, other factors including transmural heterogeneity of myocardial repolarization also play a role in the genesis of TdP. A meta-analysis indicated that the chance of developing TdP is substantially low, and there is an inconsistent relationship between QT prolongation and TdP (19). Therefore it can be emphasized that there is an incomplete and complex relationship between prolongation of the QTc interval and the risk of developing TdP. In support of this complex interaction, a recent study found that TdP occurred even in COVID-19 patients with a QTc<500 ms (20). Also, regarding the iCEB we investigated in our study, we found a significant iCEB increase in addition to significant QT and QTc prolongation without any ventricular arrhythmias in a short-term HCQ treatment. It is plausible that although HCQ has the potential to significantly prolong repolarization parameters in ECG, it may be rarely leading to the occurrence of TdP. Since it is known that TdP has some established factors such as structural heart disease, female sex, advanced age congenital QT prolongation, electrolyte disorders, and baseline QTc prolongation, we believe that HCQ should be used more carefully with these conditions or using other QT-prolonging agents such as macrolide antibiotics (21,22).

Limitations

There are several limitations to our study. Firstly, this was a retrospective study and the sample size was relatively small, especially regarding the prognostic value of the studied parameters. Secondly, it lacked Holter monitoring or telecardiography to more accurately detect ventricular arrhythmias. Thirdly, a single researcher evaluated the ECG parameters manually using a magnifying glass; thus, intraobserver variability was not evaluated for QTc and iCEB. Also, using an automated ECG measurement method might have been more effective in reducing measurement errors. Fourthly, only suspected COVID-19 patients were enrolled and the HCQ treatment duration was short. And lastly, there was no data regarding the long-term mortality and morbidity effects of HCQ treatment.

CONCLUSION

HCQ causes an increase in iCEB, QT, and QTc in ECG, most notably after the loading dose. It can be suggested that it appears safe for a short time in those without myocardial substrates or other risk factors for ventricular arrhythmias related to QT and/or QTc prolongation. iCEB may be a useful parameter for evaluating the TdP risk for those treated with HCQ and should be further studied in prospective randomized controlled studies

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Başkent University Non-Interventional Clinical Research Ethics Committee (Date: 2021, Project No: KA20/227, Decision No: 21/127).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The effect of prophylactic vitamin C use on COVID-19 infection

Hafize Kızılkaya[1], Vedat Gençer[2]

[1]Yozgat Bozok University, Faculty of Medicine, Department of Internal Medicine, Yozgat, Turkey
[2]Yozgat Bozok University, Faculty of Medicine, Department of Nephrology, Yozgat, Turkey

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ABSTRACT

Aim: In vitamin C deficiency, the immune system deteriorates and the body becomes more susceptible to infections. Since vitamin C levels will decrease significantly in infectious conditions due to increased metabolic requirements, the daily need for vitamin C increases. In our study, it was aimed to investigate the effects of 500 mg and more vitamin C intake on COVID-19 infection during the pandemic process.

Material and Method: A group consisting of 100 participants who received vitamin C supplements at a daily dose of at least 500 mg daily for a minimum of 1-3 months in their diet and a control group of 100 people who did not receive vitamin supplements were included in the study. While determining the amount of Vitamin C intake of the participants; The amount of Vitamin C in oral food supplements or foods containing vitamin C in their diets (orange, tangerine, grapefruit, kiwi, pineapple, strawberry, lemon, red and green peppers, tomatoes, arugula, parsley, greens such as lettuce, fresh rosehip, broccoli, cabbage, spinach) The vitamin level was calculated according to the amount of vegetables (such as vegetables). None of the participants had side effects suggestive of vitamin C toxicity. Besides the height, weight, gender, age, known illness and other demographic data of all participants; COVID-19 disease status, contact with COVID-19 patients, and whether or not they had a COVID infection after contact were examined. In addition, data on the presence of symptoms, severity and duration of the disease were noted in patients with COVID-19 infection, and both groups were compared statistically in terms of results.

Results: In the group receiving less than 500 mg daily; COVID-19 infection symptoms, respiratory distress, disease severity were found to be higher, and the symptoms were found to be more aggressive. While total contact and high-risk contact at all levels was higher in the group that received more than 500 mg of vitamin C daily, the rate of being COVID was lower compared to the other groups.

Conclusion: One of the most effective precautions to be taken to increase body resistance against COVID-19 is adequate vitamin C intake. In the study, it has been shown that adequate vitamin C taken with both food and nutritional supplements reduce the risk of getting COVID-19, reduce the risk of severe respiratory distress on COVID-19, as well as reduce both symptoms and symptom duration.

Keywords: COVID-19, prophylactic vitamin C, COVID-19 violence

INTRODUCTION

Vitamin C (ascorbic acid) is one of the essential water-soluble nutrients. It is synthesized from fructose in plants and glucose in animals. Since it is not synthesized in humans, it must be taken from outside (1). The immune system is a specialized, versatile mechanism developed to protect the body from pathogens. It is divided into congenital immunity and acquired immunity (2). For nearly fifty years, it has been stated that vitamin C has a very important role, especially in the function of immune system cells (3). The recommended daily intake of vitamin C is 110 mg/day for men and 95 mg/day for women (4). However, in a person exposed to infectious agents and under physical stress, this amount may be insufficient. In order to meet the nutritional needs of the general population and especially adults aged 65 and over, 200 mg of supplements per day is recommended. In addition, it recommends 400 mg per day for individuals 50 years+ of age to strengthen the immune system (5).

Corresponding Author: Hafize Kızılkaya, hfz.kizilkaya@gmail.com
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To date, 7 corona viruses with respiratory tract involvement have been identified in human beings (HCoVs). Effective in COVID is considered to be beta-CoVs (6). Culture, electron microscopy and serological tests are used for diagnosis. There are four types of proteins called spike (S), envelope (E), membrane (M) and nucleocapsid (N) that participate in the structure of the virus. The S protein enables the viral genome to enter the cell by establishing a connection between the cell it will affect and the virus. E and M proteins participate in the transmembrane structure. Nucleocapsid (N) is used in the cloning and production of recombinant proteins (7).

There is no treatment for COVID-19 yet. Vitamin C has become a potentially helpful *Candida*te for COVID-19 treatment due to its antioxidant, anti-inflammatory and immunomodulatory properties. To date, oral vitamin C has been shown to reduce both the duration and frequency of respiratory infections. In addition, intravenous vitamin C has been shown to reduce hospital stay, stay in mechanical ventilation and intensive care, and reduce mortality. The benefits of using vitamin C in COVID-19 have been shown due to the low cost of vitamin C, the high safety profile, and the increased need for vitamin C during inflammation (5). The need for vitamin C has increased during viral infections such as COVID-19. In these cases, the amount required to keep vitamin C within normal plasma levels has been determined as 2-3 g/day (8). Studies have shown that low vitamin C is associated with high oxidative stress. Since vitamin C is reduced in cases of pneumonia and sepsis, studies have been conducted showing the effectiveness of vitamin C in these groups (9). Our aim in this study; to investigate the effects of the amount of vitamin C taken orally on COVID-19 symptoms, duration and severity of symptoms.

MATERIAL AND METHOD

This study was approved by Yozgat Bozok University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.12.2020, Decision No: 2017-KAEK-189-2020.12_06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients over the age of 18 who applied to Yozgat Bozok University Medical Faculty internal medicine outpatient clinics were included in our study. The diet of the patients was questioned and evaluated according to their prophylactic vitamin C content during the pandemic process.

When calculating the amount of vitamin C in the diet of the patients, the foods containing vitamin C in the food supplement or diet (orange, tangerine, grapefruit, kiwi, pineapple, strawberry, lemon, red and green pepper, tomato, arugula, parsley, lettuce, fresh rosehip, broccoli, cabbage considering the amount of spinach) were included in the study.

Accordingly, the participants were divided into two groups as patients with or without vitamin C at a daily dose of at least 500 mg (10) between 1-3 months on a regular basis. In addition to the height, weight, gender, age, known disease and other demographic data of all participants, COVID-19 disease status and contact with COVID-19 patients were evaluated.

Accordingly, people in intensive contact with COVID-19 patients wearing a Medical (Surgical) mask;

- if all personal protective equipment (PPE) was used properly considered as risk-free,
- if not wearing gloves and gowns or eye protection considered as low risk,
- if not used medical mask or N95 or medical mask in case of N95 indication considered as medium risk.

The data obtained from the questionnaires containing data on the condition of the same participants after contact with COVID-19, and the disease symptoms of patients with COVID-19, the severity and duration of the disease were noted and statistically compared in terms of both groups (11).

RESULTS

Of the two hundred participants in the study, 52.5% (n=105) were female and 47.5% (n=95) were male. The average age was 44.18 years, average height 168.21 cm, average weight 75.83 kg, and body mass index 26.79 kg/cm².

100 (50%) of were using 500 mg or more prophylactic oral vitamin C daily. Among all participants, the rate of getting COVID-19 disease was 52.5%, and the frequency of symptoms in those with COVID was 49.5%.

Any statistically significant difference was found between the groups (receiving 500 mg or more prophylactic oral vitamin C per day (n=100) and less than 500 mg (n=100)) in terms of age, gender, height, weight, BMI, smoking and alcohol use, and being COVID-19 ($p > 0.05$).

When both groups are evaluated in terms of chronic diseases; while there was no significant difference in terms of hypertension, chronic renal failure, chronic heart disease, asthma ($p>0.05$); those with chronic obstructive pulmonary disease were more in the vitamin C group; and the number of patients with diabetes mellitus was higher in the group not receiving vitamin C supplements ($p<0.05$) (**Table 1**).

While 46% of the patient group who received 500 mg and more prophylactic oral vitamin C per day became COVID, this rate was 59% in the group receiving less than 500 mg per day. COVID-19 ratio was similar in both groups (p=0.066). Disease duration, COVID symptoms, respiratory distress, and disease severity were found to be significantly higher in the group receiving less than 500 mg daily (p<0.05). In the group receiving more than 500 mg of vitamin C per day, 86.9% of the patients who had COVID-19, and 100% of the patients in the group receiving less than 500 mg per day showed symptoms. In addition, when the symptomatic ones are evaluated within themselves; while most of the people who take more than 500 mg of vitamin C per day have mild symptoms; those taking vitamin C below 500 mg per day were found to have the majority of moderate symptoms. Education level and income level were similar between the groups (p>0.05) (**Table 2**).

While total contact at all levels was 74% and high-risk contact was 42% in the group receiving more than 500 mg of vitamin C daily, this rate was found to be 52% and 28%, respectively in the group receiving vitamin C below 500 mg per day. In the group that received more than 500 mg of vitamin C daily, the contact rates were found to be significantly higher than the other group (p<0.05) (**Table 3**).

DISCUSSION

In this study, daily prophylactic oral vitamin C intake of 500 mg and above; although there was more contact with COVID and there was a higher risk of contact, the rate of becoming COVID afterwards was found to be significantly lower than the group with a vitamin C intake of less than 500 mg. In addition, it was observed that individuals who took 500 mg and more vitamin C had COVID, their symptoms were milder and the symptom duration was shorter.

The RNA virus called Coronavirus 2 (SARS-CoV-2) causes COVID-19 disease. Coronaviruses take their name from surface proteins called corona (crown) to bind and penetrate host cells (13). It may be asymptomatic or cause serious complications such as flu symptoms, fever, cough, gastrointestinal system symptoms, shortness of breath, pneumonia, respiratory failure and kidney failure. It also has a 3% mortality (14).

Vitamin C has many roles such as energy metabolism, collagen synthesis and repair, adrenal steroid, catecholamine production, iron absorption. In addition, it reduces the risk of infection due to its antimicrobial, immunomodulatory and antioxidant properties (15). Vitamin C protects the mucosal barrier by reducing viral adhesion (16). It has been shown that individuals with

Table 1. Demographic and clinical parameters of groups receiving 500 mg or more daily and less than 500 mg daily oral vitamin C

Properties	Vitamin C		P
	Daily 500 mg and more (n=100)	Daily less than 500 mg (n=100)	
Age	45.37±15.31	43.00±16.01	0.286
Gender (m/f)	51/49	44/56	0.322
Height (cm)	168.68±8.86	167.74±8.77	0.452
Weight (kg)	75.60±13.82	76.07±17.51	0.833
BMI(kg/cm²)	26.65±5.14	26.92±5.43	0.322
Cigarettes (%)	29	25	0.524
Alcohol (%)	6	4	0.516
COVID-19 (%)	46	59	0.066

BMI: Body mass index

Table 2. Comparison of the effects of oral prophylactic vitamin C supplementation on COVID-19 infection and comparison of education and income levels

COVID-19 Data	Vitamin C		P
	Daily 500 mg and more (n=100)	Daily less than 500 mg (n=100)	
Respiratory distress			0.031
No infection	48	44	
Nasal O_2 taken	8	2	
CPAP taken	1	0	
Intubated	2	0	
Disease duration			<0.05
<1 day	1	10	
1-3 days	1	16	
3-7 days	15	14	
7-14 days	23	6	
>14 days	19	0	
Disease severity			<0.05
No Infection	0	1	
Mild	7	34	
Medium	27	11	
Severe	25	0	
Disease symptoms			0.012
None	0	6	
Infected	59	40	
Income level			0.55
Low	29	15	
Medium	24	27	
High	47	58	
Education level			0.60
Primary	27	14	
Secondary	11	19	
College	53	61	
Masters	9	6	

CPAP: Continuos positive airway pressure, O_2: Oxygen

Table 3. Effects of prophylactic oral vitamin C supplementation on COVID-19 infection

COVID-19	Contacted				P
Vitamin C	None	Low	Medium	High	
Infected					<0.05
Daily less than 500 mg	37	2	1	1	
Daily 500 mg and more	19	9	5	21	
Not infected					<0.05
Daily less than 500 mg	11	7	14	27	
Daily 500 mg and more	7	3	12	21	

low dietary intake of vitamin C have a reduced risk of pneumonia with oral vitamin C supplements (17). In our study, the symptoms of those who took 500 mg or more prophylactic vitamin C were mild. This suggests that for those who take higher doses of vitamin C, mucosal viral transmission may be prevented, resulting in less viral load and, consequently, COVID-19 symptoms are milder. In addition, the duration of symptoms was found to be significantly lower in the vitamin C group in our study. It may be due to the antimicrobial, immunomodular effects of vitamin C.

Vitamin C is very important for immunity. The efficacy of chemokines, cytokines, adhesion molecules, inflammatory mediators and apoptosis inhibitors in the immune system has been demonstrated. While inhibiting the production of IL-6 and tumor necrosis factor alpha (TNF-α), GM-CSF may decrease the signal response. Tine vitamin C helps regulate the proliferation and functioning of T and B cells and natural killer (NK) cells and prevents the cytokine storm from progressing. Oxidative stress has a damaging effect on viral respiratory infections. With vitamin C, the response to oxidative stress increases. The role of oxidative stress in the mechanism of COVID-19 has been emphasized (16). Oxidative stress, immunological damage, endothelial and alveolar membrane damage have been reported in the mechanism of COVID. In the pathophysiology of the progression to Covi19 pneumonia and respiratory failure, the excessive response of the immune system involving IL-6 and endothelin-1 (ET-1) is involved (18). Considering these mechanisms, many treatment regimens that can affect different pathways for Covi19 treatment have been tried. Due to its effect on reducing both COVID and non-COVID hyperinflammation, intravenous vitamin C administration has also taken its place among these regimens. Due to its antioxidant, anti-inflammatory, antithrombotic and immunomodulatory aspects, high amounts of intravenous vitamin C were administered to normalize plasma levels, especially in patients with critically ill sepsis, and it has been shown to reduce mortality (9).

Again in clinical studies; In patients diagnosed with acute respiratory distress syndrome (ARDS) and sepsis, it has been shown that there is a variable degree of effectiveness in cytokine storm with the administration of high doses of intravenous vitamin C. Therefore, it was thought that it could be added to the treatment of ARDS and the treatment of multiorgan dysfunction associated with COVID (16). In our study, respiratory distress was found to be higher in the group that did not take sufficient vitamin C, and the rate of patients who received CPAP and was intubated was higher in this group.

Previous publications on intravenous vitamin C included the results of the application after the diagnosis of COVID-19. Given that vitamin C has substantial evidence on immunity and is also cheap and safe, it was thought that the use of oral prophylactic could be beneficial and the (very) high-dose regimen could be beneficial in severe cases of Covi19, but clinical studies were expected to provide more conclusive evidence (18).

Our study has some limitations. First, the small number of patients, and secondly, the participants were not questioned in terms of other vitamins and minerals that affect immunity. Although the COVID-19 contact of the patients is questioned, the information given about the contact of the patients may not give a definite result due to the asymptomatic COVID-19 cases.

In addition, there might be individuals who stated that they did not have COVID-19 because they were asymptomatic, and those who are misdiagnoses caused by false negative results of the PCR test.

CONCLUSION

In our study, the effects of prophylactic oral use of vitamin C on COVID were investigated. We need to take measures to strengthen the immune system against COVID infection, which has a wide range of symptoms. One of these measures is adequate vitamin C intake. Adequate vitamin C supplements taken with foods and nutritional supplements; has been shown in our study that reduces the risk of getting COVID after contact, reduces severe respiratory distress in those with COVID, and also reduces both symptoms and symptom duration. Previously, publications on intravenous vitamin C included the results of the application after the diagnosis of COVID. Considering that vitamin C has substantial evidence on immunity and is also cheap and safe, oral prophylactic use may be beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Yozgat Bozok University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.12.2020, Decision No: 2017-KAEK-189-2020.12_06).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review of COVID-19 vaccinated patients' emergency room admissions

Ensar Durmuş, Necip Gökhan Güner, Fatih Güneysu, Nuray Aslan, Yusuf Yürümez
Sakarya University Training and Research Hospital,Department of Emergency Service, Sakarya, Turkey

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ABSTRACT

Introduction: This study was aimed to define the demographic structure of vaccinated patients admitted to the emergency room (ER) with COVID-19 symptoms, and their hospitalization status, length of stay (LoS) in hospital, and mortality status.

Material and Method: This research is a retrospective, cross-sectional and descriptive study. Furthermore, it includes the period between 15.01.2021 and 30.04.2021.

Results: An 887 COVID-19 vaccinated patients who applied to ER. Of these, 383 (42.2%) were male, and 504 (56.8%) were female. The mean age of the patients was 52±18.6 years. The number of single-dose vaccinated patients was 696 (78.5%), and the two-dose vaccinated was 191 (21.5%). CoronaVac (Sinovac Life Sciences) vaccine was applied to 755 (85.1%), and BNT162b2 (Pfizer & Biontech) vaccine was applied to 132 (14.9%) patients before.

In 317 (35.7%) cases, reverse transcription-polymerase chain reaction (Rt-PCR) positivity was detected in the ER application after vaccination. Of the total patients, 86 (9.7%) were hospitalized, 14 (1.4%) patients died in the hospital.

The mean time between vaccination and application to ER was 25 (±21.9) days. Also, this period was 28.1 (±18) days in two-dose vaccinated patients.

Conclusion: People who are vaccinated with the COVID-19 vaccine continue to have hospital admissions with COVID-19 symptoms. Rt-PCR positivity, need for hospitalization, and mortality may continue to be seen in vaccinated individuals.

Keywords: Pandemic, COVID-19, vaccine, emergency room

INTRODUCTION

Since the World Health Organization (WHO) declared the COVID-19 pandemic in March 2020, health officials have been looking for a method to combat this disease (1). On the one hand, measures were taken to reduce the spread of the virus, such as social isolation, wearing masks, public transportation regulations, and curfew; on the other hand, investigations were conducted to treat infected cases (2,3). Although many drugs have been used to manage the disease in the early days, there is still no definitive method to treat the infection (4).

The high mortality rate in hospitalized patients, the long hospitalization period of the patients, the significant rate of patients in need of intensive care, and the extensive mortality have pointed that other resolutions should be queried. As a solution, COVID-19 vaccine research has been initiated globally and has progressed rapidly (5).

It is unknown exactly what effect the mutant viruses will have on vaccines when the SARS-CoV-2 virus mutates (6). It is troubling that the progress in potential virus pathogenicity due to mutations will create challenges in drug and vaccine improvement levels (7). On the other hand, a suitable vaccine is demanded to help fight disease; furthermore, especially to have a protective effect against severe diseases and mortality (8).

Vaccination programs against COVID-19 have commenced in Turkey since January/2021. In the first place, healthcare workers, immunosuppressed patients, cancer patients, and the elderly population were vaccinated with the inactive CoronaVac vaccine (Sinovac Life Sciences). Later, mRNA vaccines BNT162b2 (Pfizer& Biontech) were added to the vaccine program, leaving the patient preference. As of 30.04.2021, Turkey has risen to sixth place among the countries that have applied the most COVID-19 vaccine globally, and it has applied the first dose to 13,715,749 people and the second dose to 9,107,089 people (9,10).

Corresponding Author: Fatih Güneysu, fatihguneysu55@hotmail.com
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In this study, the general characteristics of the patients who were vaccinated with CoronaVac or BNT162b2 vaccines in Sakarya Province of Turkey and administered to Sakarya Training and Research Hospital (SEAH) emergency room (ER) were examined. It is aimed to define the demographic structure of patients admitted to the ER with COVID-19 symptoms after vaccination, hospitalization status, length of stay (LoS), and mortality. In this way contribute to the current medical literature with a limited number of publications on this subject.

MATERIAL AND METHOD

The study protocol was approved by the Sakarya University Faculty of Medicine Non-Interventional Ethics Committee (Date: 28.04.2021, Decision No: 310). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Type

This research is a retrospective, cross-sectional and descriptive study. Furthermore, it includes the period between 15.01.2021 and 30.04.2021.

The study sample was the patients who presented to the SEAH adult ER with COVID-19 symptoms after being vaccinated with CoronaVac or BNT162b2. The study population was the vaccinated patients who applied to the ER with the findings of COVID-19.

Definitions

CoronaVac is an inactive vaccine, and BNT162b2 is an mRNA vaccine, and these vaccines are applied in two doses. By the Ministry of Health's vaccine application strategy, vaccines are applied in two doses at four-week intervals (11). Primarily, healthcare workers, people living in elderly nursing homes, and older adults over 65 were vaccinated in Turkey (11).

Fever, cough, dyspnea, sore throat, headache, myalgia, loss of taste and smell, or diarrhea have been affirmed as COVID-19 symptoms (12). Rt-PCR was analyzed by taking oropharyngeal and nasopharyngeal combined swabs in all cases with COVID-19 symptoms. Only patients with a positive Rt-PCR test were recognized positive in the study.

Inclusion Criteria

Among patients vaccinated with at least one dose of CoronaVac or BNT162b2, the following were included in the study:

- Patients aged 18 and over,
- Patients with at least one COVID-19 symptom,
- Patients admitted to the XEAH ER,
- Patients whose information could be accessed fully from the hospital automation system.

Exclusion Criteria

- Patients younger than 18 years old,
- Pregnant patients,
- COVID-19 patients who have never been vaccinated with COVID-19 vaccines,
- Patients who applied to the ER with a complaint other than COVID-19 symptoms,
- Patients whose information could not be fully reached were excluded from the study.

Data Collection

The data of the cases that applied to the XEAH ER during the study period was reached from the hospital automation system and patient files. Patients' age, gender information, the name of the applied vaccine, the number of vaccine's dose, the time between vaccination and admission to the ER, Rt-PCR positivity after vaccination, hospitalization status, length of stay (LoS) in hospital, and mortality status of the inpatients were retrospectively scanned.

Statistical Analysis

The collected data were analyzed with the IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp. Released 2012, Armonk, NY: IBM Corp.). Skewness and Kurtosis results were verified to be in the range of -2/+2 for the data's normal distribution (13). Chi-square test was utilized for comparison of categorical data, and resulted with $p<0.05$ were accepted statistically meaningful.

An independent t-test was applied to compare two independent data groups that were normally distributed, and results with $p<0.05$ were considered significant.

RESULTS

An 887 COVID-19 vaccinated patients who applied to ER with COVID-19 symptoms were included in the study. Of these, 383 (42.2%) were male, and 504 (56.8%) were female. The mean age of the patients was 52 (±18.6) years, the median value was 56, and the age range was between 20-94 years.

The number of single-dose vaccinated patients admitted to the ER was 696 (78.5%), and the number of two doses vaccinated patients admitted was 191 (21.5%). The Coronavac vaccine was applied to 755 (85.1%) of the patients; the BNT162b2 vaccine was also applied to 132 (14.9%).

In 317 (35.7%) cases, Rt-PCR positivity was detected in the ER application after vaccination. Of the total patients, 86 (9.7%) were hospitalized; furthermore, 14 patients (1.4%) died during the treatment in the hospital.

The mean time between vaccination and application to ER was 25 (±21.9) days, and the median value was 18 days. This period was 28.1 (±18) days in two-dose vaccinated patients, and the median value was 26 days. The time to apply to ER was longer in those who were vaccinated with two doses.

The patients's gender and mean age, post-vaccination Rt-PCR positivity, hospitalization and mortality status were compared in **Table**. Accordingly, no significant relationship was observed between the patients' gender and their PCR positivity or hospitalization status (respectively; x2=1.665, SD=1, p=0.197 and x2=1.806, SD=1, p=0.179). There was a significant difference between the genders and the mortality status that mortality was higher in male patients (x2=4.627, SD=1, p=0.031). According to the independent t-test results, Rt-PCR positive patients' mean age (mean=57, SD=17) was found to be significantly higher than Rt-PCR negative patients' mean age (Mean=49, SD=18.9) [t(714)=-5.69, p=0.001]. In addition, hospitalized patients' mean age (mean=69, SD=9.9) was seen to be significantly higher than the outpatients (Mean=50, SD=18.3) [t(157)= -15, p<0.001]. Also, the mean age of the patients with mortality (mean=71, SD=11.9) was found to be statistically significantly higher than the surviving patients (mean=52, SD=18.5) [t(14)=-5.87, p<0.001].

Of those vaccinated with a single dose of Coronavac vaccine, 9 (1.6%) died, while two (1.1%) of those vaccinated with two doses. Similarly, no significant difference was observed in hospitalization status and Rt-PCR test positivity between those vaccinated with a single or two doses of the Coronavac vaccine (respectively; x2=0.337, SD=1, p=0.561; x2=0.863, SD=1, p=0.353).

When 14 ex-cases were examined, it was noticed that all of them were Rt-PCR positive, 12 of them were vaccinated in a single dose, and they presented to the hospital after an average of 20.5 (±14.2) days after the first dose of vaccination. In addition, the average LoS in the hospital was determined to be 8 (±4.1) days. 11 of dead patients were vaccinated with the CoronaVac vaccine and 3 with the BNT162b2 vaccine, but it was affirmed that there was no notable variation in mortality between vaccines (p=0.450).

DISCUSSION

Studies on hospital admissions of patients with the COVID-19 vaccine are limited in the medical literature. In a study conducted in the same region in the first months of the pandemic, 169 COVID-19 patients admitted to the ER and hospitalized were examined, and the average age of the patients was 64.3 (± 17.6) years (14). Additionally, in the same study, 56.2% of the hospitalized patients were reported to be male (14). The average age of the hospitalized patients in our study was 69.3 years (± 9.4 years), and 53.8% were women. Accordingly, it can be thought that the average age of the patients hospitalized from the ER after vaccination increased, and the rate of hospitalization of women increased. However, it can be said that giving priority to those aged 65 and over in the vaccination program causes the average age to be high. However, as of 26.04.2021, 47% of COVID-19 patients who were recently hospitalized in the USA were 60 years old and over. Moreover, 56% of these cases were female, consistent with our study results (15).

Our study observed that the Rt-PCR positivity rate of vaccinated patients who applied to the ER with COVID-19 symptoms was 35.7%. This Rt-PCR positivity rate may appear to be high compared to a vaccinated population. However, the rate of two-dose vaccinated Rt-PCR positive patients was among all patients was 8.3%.

Among all vaccinated patients, the hospitalization rate of those who applied to the ER was 9.7%, and the mortality rate was 1.58%. The mortality rate among hospitalized patients was found to be 16.3%. In a study conducted in the USA, it was reported that 21% of COVID-19 patients who were hospitalized resulted in mortality (16). In addition, Wenjie et al. found that the mortality rate in hospitalized COVID-19 cases was 25% (17).

Table. Comparison of patient data by gender and age average

Parameter		Rt-PCR					Hospitalization					Mortality				
		Positive		Negative		Statistical value	Yes		No		Statistical value	Ex		Alive		Statistical value
		n	%[a]	N	%[a]		n	%[a]	n	%[a]		n	%[a]	n	%[a]	
Gender	Male	146	16.5	237	26.7	p=0.197[b]	43	4.8	340	38.3	0.179[b]	10	1.1	373	42.1	0.031[b]
	Female	171	19.3	333	37.5		43	4.8	461	52		4	0.5	500	56.4	
Doses	1	243	27.4	453	51.1	p=0.328[b]	64	7.2	632	71.3	p=0.337[b]	12	1.4	684	77.1	p=0.746[c]
	2	74	8.3	117	13.2		22	2.5	169	19.1		2	0.2	189	21.3	
Vaccine Name	CoronaVac	269	30.3	486	54.8	p=0.871[b]	79	8.9	676	76.2	p=0.065[b]	11	1.2	744	83.9	p=0.450[c]
	BNT162b2	48	5.4	84	9.5		7	0.8	125	14.1		3	0.3	129	14.5	
Average Age		57		49		p=0.001[d]	69		50		p=0.001[d]	71		52		p=0.001[d]

[a]: It is the ratio of all vaccinated patients, [b]: Pearson Chi-Square test, [c]: Fisher's Exact test, [d]: Independent t-test

When compared with the mortality rates of hospitalized Covid-19 patients in the literature, it can be said that the mortality rate of vaccinated patients was few.

Patients vaccinated with the BNT162b2 vaccine appear to have fewer ER admissions, hospitalizations, and lower mortality than those vaccinated with the Coronavac vaccine. This situation is controversial whether the Coronavac vaccine was applied more in the community during the study period or whether the BNT162b2 vaccine was more protective than Coronavac. There is a need for further studies on this subject as vaccination becomes more widespread in the population.

Limitations

The study included patients who applied to SEAH ER as a single-center, and the fact that the patients may have applied to another hospital was the limitation of the study.

CONCLUSION

People who are vaccinated with the COVID-19 vaccine continue to have hospital admissions with COVID-19 symptoms. Rt-PCR positivity, need for hospitalization, and mortality may continue to be seen in vaccinated individuals. However, it will be possible to have a more precise opinion with new studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Sakarya University Faculty of Medicine Non-Interventional Ethics Committee (Date: 28.04.2021, Decision No: 310).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The predictive value of bleeding score on the diagnosis of Von Willebrand disease in children applied to the hematologic clinic with epistaxis

Ayşegül Alpcan[1], Serkan Tursun[1], Yaşar Kandur[1], Mustafa Çağlar Yörgüç[2], Meryem Albayrak[3]

[1]Kırıkkale University, School of Medicine, Department of Pediatrics, Kırıkkale, Turkey
[2] Medicana International Hospital, Department of Pediatrics, Ankara, Turkey
[3] Kırıkkale University, School of Medicine, Department of Pediatric Hematology and Oncology, Kırıkkale, Turkey

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ABSTRACT

Aim: Epistaxis may be a symptom of an inherited bleeding disease.. We aimed to analyze an approved pediatric bleeding score (PBS) as a screening test for von Willebrand Disease (VWD) in children with epistaxis

Material and Method: We retrospectively reviewed the medical records of pediatric patients, who applied to the Pediatric Hematology Department with the complaint of epistaxis between January 2018 and December 2019.

Results: One hundred and sixty eight patients enrolled in this study There were 65(38.7%) girls and 103(61.3%) boys, with a mean age of 114±49 months (range 8 months to 18 years).The PBS of 34 patients was greater than/ or equal to 2. Factor 8, von Willebrand factor antigen, and von Willebrand Ristocetin cofactor levels were significantly lower in patients with PBS≥2 compared to those in patients with PBS<2 (%73±43 vs % 91±29, p=0.03; 87±44 vs 106±29 IU/dl, p=0.03; 72±39 vs 98±30 IU/dl, p=0.001, respectively). While 15 (44%) of 34 patients with PBS ≥ 2 diagnosed VWD, but in the group with PBS<2, VWD was diagnosed for only 4 children (0.02%) (4/134). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PBS for diagnosis of VWD was 79.0%, 87.2%, 44%, and 97% respectively.

Conclusion: PBS could be integrated into the evaluation of children suspected of having a bleeding disorder such as VWD in pediatrician's offices. Our cut off value 2 appears to be significant in exclusion of VWD, since its high negative predictive value.

Keywords: Pediatric bleeding score, epistaxis, Von Willebrand disease

INTRODUCTION

Epistaxis is a common problem in the pediatric population and it can cause serious distress and anxiety among children and their parents. It may be a symptom of an inherited bleeding disease (1). Von Willebrand Disease (VWD), is a disease associated with bleeding diathesis especially epistaxis that is the most common symptom (2). Determining bleeding in diagnosing of VWD often poses a significant challenge in children. However, children may present epistaxis without the disease. Therefore, a coagulation test should not be performed on every patient with epistaxis and VWD should not be considered immediately. This standardization aims primarily to avoid unnecessary laboratory tests and to predict future risk of bleeding. For this reason, development of bleeding assessment tools has been studied in recent years to help to measure bleeding symptoms and to standardize bleeding histories (3,4). Bowman et al. established and approved pediatric bleeding score (PBS) in 2009 to detect VWD. The PBS examine the presence and severity of bleeding symptoms including epistaxis, bleeding from minor wounds, easy bruising, oral cavity bleeding, bleeding after dental or surgical procedures, gastrointestinal tract bleeding, menorrhagia (5). The patient is questioned for epistaxis, easy bruising, bleeding after dental or surgical procedures and menorrhagia (6). Scoring is based on a scale from 0 to 4 in most categories, and -1 to 4 in some categories, with representing the most severe symptoms (7). When PBS was administered to children with bleeding symptoms, the sensitivity and specificity for VWD were 83% and 79% respectively and the negative predictive value (NPV) was 99% (5). In this study, we aimed to confirm PBS as a VWD screening tool in children with epistaxis admitted to the pediatrics hematology clinic of a tertiary referral hospital in middle Anatolia of Turkey.

Corresponding Author: Ayşegül Alpcan, ozcalk@yahoo.com
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MATERIAL AND METHOD

The study protocol was approved by the Kırıkkale University School of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 07.08.2019, Decision No: 2019.08.05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We retrospectively reviewed the medical records of pediatric patients, who applied to the pediatric hematology department with the complaint of epistaxis between January 2018 and December 2019. Data including demographic characteristics, medical history and family history of bleeding were recorded. Bleeding scores of all children were calculated. Following the physical examination, laboratory tests were performed: complete blood count, peripheral smear, blood type, bleeding time, prothrombin time (PT), partial thromboplastin time (aPTT), von Willebrand factor antigen (VWF:Ag) levels, Factor VIII (FVIII) level, and platelet function were analyzed with platelet function analyzer (PFA-100). The in-house enzyme-linked immunosorbent assays were applied for VWF:Ag as previously described (8). The in-house VWF ristocetin cofactor (VWF:RCo) assay (9) was performed to measure GpIb binding activity. FVIII coagulant activity (FVIII:C) assay (10) was conducted.

In this study, the participants with VWF levels, activities and/or antigen, of <30 IU/dL were diagnosed as VWD (11). The patients with VWF levels of 30 to 50 IU/dL would be reclassified into low VWF according to the current concept (12). The patients with insufficient clinical information, acquired von Willebrand syndrome (AVWS), or diagnosis as other bleeding disorders rather than VWD were excluded. Patients with an organic pathology detected on ear, nose and throat examination, who used drugs, who had a primary disease leading to bleeding diathesis, traumatic epistaxis and the patients with hypertension were excluded from the study.

Pediatric Bleeding Score (PBS)

The patients evaluated with a total bleeding score equal and bigger than 2 accepted as having a bleeding disorder (5). The questions were answered by the parents of children, and also by themselves of the children aged 12 years and older. Patients were classified into two groups based on the PBS as follows: PBS bigger than/ or equal to 2 and PBS smaller than 2.

Statistical Analysis

SPSS for Windows (Version 16, USA) was used for data management and statistical analysis. The normality evaluation of the data was done with Shapiro Wilk test. The continous variables were presented as mean±SD and the categorical variables were presented as number (percentage). The comparison of continuous variables between two groups were done with student t test or Mann Whitney U test according to distribution normality of data and categorical variables were compared between two groups with Chi Square test. Sensitivity, specificity, and positive and negative predictive value of PBS score for the diagnosis of VWD were calculated. A p-value smaller than 0.05 was accepted as statistically significant.

RESULTS

One hundred and sixty eight patients enrolled in this study There were 65(38.7%) girls and 103(61.3%) boys, with a mean age of 114±49 months (range 8 months to 18 years)

The PBS of 34 patients was greater than/ or equal to 2. The mean age of these 34 patients was 110±50 months (range 24-204 months). We compared the demographic and hematological parameters of patients with PBS<2 (n=134) and PBS≥2 (n=34). Factor 8, VWFAg, and VWFR co levels were significantly lower in patients with PBS≥2 compared to those in patients with PBS<2 (%73±43 vs % 91±29, p=0.03; 87±44 vs 106±29 IU/dl, p=0.03; 72±39 vs 98±30 IU/dl, p=0.001, respectively). The remaining demographic and hematological parameters did not show a significant difference between patients with either PBS≥2 or not (**Table 1**).

Table 1. Demographic and hematological parameters of the study population

Parameter	Pediatric bleeding score<2 n=134	Pediatric bleeding score≥2 n=34	P value
Age (months)	115±49	110±50	0.6
Female/Male (n/n)	51/83	14/20	0.84
Platelet (x10^3)	302±71	322±72	0.18
Hemoglobin (gr/dL)	13±1.2	12.8±1.1	0.27
Prothrombin time (seconds)	10.8±4.5	11.4±3	0.46
Fibrinogen (mg/dL)	252±65	174±87	0.16
APTT (seconds)	27±9.1	29.4±6.6	0.15
Factor VIII (%)	91±29	73±43	0.03
VWFAg (IU/dl)	106±29	87±44	0.03
VWFRCo (IU/dl)	98±30	72±39	0.001
PFA-100	109±18	127±74	0.24
Bleeding time (minutes)	2.1±1.3	4.7±3.7	0.44

APTT: Activated partial thromboplastin time, FVIII: Factor VIII, VWF:Ag: von Willebrand factor antigen, VWFRCo: von Willebrand Ristocetin cofactor

While 15 (44%) of 34 patients with PBS ≥ 2 diagnosed VWD, but in the group with PBS<2, VWD was diagnosed for only 4 children (0.02%) (4/134). The PBS, demographic characteristics, VWF, Ristocetin and Factor VIII levels of the 15 patients were given in **Table 2**. Seven of them have had the diagnosis of VWD. The remaining 8 children have taken into follow-up for the possibility of development of VWD.

Table 2. Demographic and laboratory characteristics of the Von Willebrand disease patients with pediatric bleeding score ≥2

Patient No	Age (months)	Family history	F VIII (IU/dl)	VWF-Ag (IU/dl)	VWF:Ricof (IU/dl)
1	86	+	33	50	27
2	139	-	32	43	21
3	162	-	49	50	47
4	64	-	42	20	30
5	152	+	21	51	61
6	12	+	26	34	36
7	160	-	28	90	148
8	180	+	20	16	10
9	60	+	29	41	33
10	50	-	31	72	29
11	96	-	41	16	64
12	141	-	42	114	69
13	73	-	24	39	22
14	118	+	42	46	61
15	142	+	44	59	37

The PBS, demographic characteristics, VWF, Ristocetin and Factor VIII levles of the 4 patients with PBS<2 were given in **Table 3.**

Table 3. Demographic and laboratory characteristics of 4 Von Willebrand disease patients with pediatric bleeding score <2

Patient No	Age (months)	Family history	F VIII (IU/dl)	VWF-Ag (IU/dl)	VWF:Ricof (IU/dl)
1	36	Brother+	37	135	88
2	192	-	20	40	32
3	120	-	36	49	24
4	62	Brother +	25	42	29

Number of patients with a diagnosis of VWD according to PBS scores were given in **Table 4**.

Table 4. Crosstabulation of pediatric bleeding score vs Von Willebrand disease diagnosis

Parameter	VWD (+) n=19	VWD (-) n=149
PBS ≥2 (n/%)	15 (79.0)	19 (12.8)
PBS <2 (n/%)	4 (21.0)	130 (87.2)
Total	19	149

PBS: Pediatric bleeding score

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PBS for diagnosis of VWD was 79.0%, 87.2%, 44%, and 97% respectively.

DISCUSSION

In our study, we found that the PBS cut-off value 2 is meaningful to predict VWD in pediatric patients experiencing epistaxis. According to our knowledge, this study is the first in the literature evaluating PBS in only pediatric patients with complaint of epistaxis. This study showed the effectiveness of PBS to diagnose theVWD in pediatric patients with epistaxis.

Beyond being used as a screening test in the primary healthcare services, PBSs can be used to assess and document the severity of bleeding in the referral setting and as part of the initial diagnostic approach. A meta-analytic study suggested the use of a validated PBS rather than a non-standardized clinical assessment as an initial screening test to determine who needs specific blood tests for patients with a low probability of VWD (e.g. seen in primary care setting) (13).

Previous studies showed that a clinically significant bleeding score of ≥2 can be applied in the discrimination of "normal" and "mild hemorrhagic diseases (14-16). In these studies the high NPV and receiver operating characteristic (ROC) data show that PBS can be used in advance to differentiate between VWD and normal children. Another study from our country (17) showed that the cut off level of 2 is suitable forTurkish population in differential diagnosis of "mild bleeding disorders" and "hemostatically normal patients with symptoms". Bowman et al. (5) showed that a cut off value of PBS above 2 in patients with bleeding history (bleeding from minor wounds, epistaxis, easy bruising, and menorrhagia), the sensitivity, specificity, PPV, and NPV were found to be 83%, 79%, 14%, and 99%, respectively near similar to our results. While we found a positive predictive value of 44% of the VWD in patients with PBS value of ≥2, 0.02% of patients with low PBS were diagnosed VWD. Therefore the negative predictive value of scoring was higher.

There is no single test that can diagnose VWD. Measurement of VWF antigen, von Willebrand factor ristocetin cofactor activity, factor VIII clotting activity, and measurement of VWF multimers lead to the diagnosis of VWD. Obtaining these tests in population-based screening would be not a cost-benefit analysis (18). So that PBS usage may convenient in first visit differential diagnosis of bleeding disorders, especially VWD.

We think that non-invasive clinical approaches that disable the use of invasive methods could be applied in the diagnosis of such a common autosomal dominant disease. If the bleeding history is evaluated with PBS, it will provide a prediction for advanced blood tests in selected patients. The PBS may not detect mild cases. However, due to its high NPV, it prevents unnecessary tests that is also cost-effective. By this, inappropriate laboratory testing, over-treatment and, distressing venepuncture in children would be prevented. We think that PBS can be applied in primary care medicine.

Our study has the following limitations. Firstly, its retrospective design could not indicate the true prevalence and diagnosis of VWD. And secondly this study conducted on a single center, so it could not project the true prevalence belongs to total population.

CONCLUSION

PBS could be integrated into the evaluation of children suspected of having a bleeding disorder such as VWD in pediatrician's offices. Our cut off value appears to be significant in exclusion of VWD, since its high negative predictive value. So that in patients with the suspicion of VWD and a PBS ≥2, the diagnosis should be supported by coagulation laboratory tests.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Kırıkkale University School of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 07.08.2019, Decision No: 2019.08.05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Publication rate of oral presentations presented at national pathology congresses, 5-year analysis

Aytül Buğra[1], Abdül Kerim Buğra[2]

[1]Council of Forensic Medicine, Morgue Department, Histopathology Unit, İstanbul, Turkey
[2]University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiovascular Surgery, İstanbul, Turkey

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ABSTRACT

Aim: In this study, the contribution of the oral presentations presented at national pathology congresses to the literature was investigated.

Material and Method: A total of 378 abstracts presented at national pathology congresses between 2014-2018 were scanned in PubMed and Google Academic databases. In order to determine whether these abstracts were obtained from thesis studies, they were scanned in the database of the National Thesis Center. The screening was performed simultaneously with the verbal title and authors. The abstracts were examined in terms of the study design, the type of institution where the study was conducted, whether it was a thesis study, the status of its publication in scientific journals, the type of peer-reviewed journal in which it was published, and the time from presentation to publication.

Results: 47.4% (n=179) of 378 papers were retrospective and 52.6% (n=199) were prospective studies. 73.5% (n=278) of the studies of the presentations were done in universities, 23.5% (n=89) in training and research hospitals, and 3% (n=11) in other institutions. 16.9% (n=64) of the abstracts were obtained from the thesis. A total of 27% (n=102) of the abstracts were published in a scientific journal as an article. A significant difference was found in terms of publication in prospective studies compared to retrospective studies (p=0.03). University hospitals had the highest rate (25.5%, n=71). The average period of publication of papers in a scientific journal was 15.0 ±12.3 months (0-68.9) months. 61.8% (n=63) of the abstracts were published in SCI(E) journals, 18.6% (n=19) in other international peer-review journals and 19.6% (n=20) in national peer-review journals.

Conclusion: We believe that researchers should develop not only oral presentation but also encouraging methods to transform studies into publications.

Keywords: Oral presentation, congress, pathology

INTRODUCTION

In our country, the National Pathology Congress is an important platform where hundreds of oral and poster presentations are presented every year, and up-to-date information and developments in pathology are conveyed. In these meetings attended by a large number of researchers, there are educational courses for residents and young specialists, and panels where current developments in pathology are also attended by foreign speakers. Scientific congresses are organizations where a large number of researchers come together to strengthen social relations as well as scientific relations. The National Pathology Congress is organized in a different city each year in our country and by a different working group.

Abstracts sent to be presented at the congress usually have a certain word limit. Therefore, the abstracts in the proceedings abstract book contain the main lines of the study. Case selection, method, and statistical analysis cannot be adequately included in the abstracts, and the findings and the results obtained cannot be mentioned in detail. The results of the abstracts that are not published may not reach the potential readership and contribute to the literature adequately (1). The high publication rate of oral presentations presented in scientific congresses is also an indicator of the high scientific quality of the congress (2).

There is no data on the publication rate of oral presentations presented in the National Pathology

Corresponding Author: Aytül Buğra, aytulsargan@gmail.com
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Congress in peer-reviewed journals. In this study, we aimed to investigate the publication rate of oral presentations presented at national pathology congresses and their contribution to the literature.

MATERIAL AND METHOD

In our study, only open access data were used, therefore, ethics committee approval was not required. In similar studies about the publication rate in the literature, an average of 20 months of follow-up period following oral presentations was sufficient for the first results. We included the 5-year national pathology congresses between 2014 and 2018 in our study, and the cut-off date was December 2020. We obtained the abstracts submitted between 2016-2018 from the official website of the Journal of Current Pathology (http://guncelpatoloji.org/) and the other years' from the congress abstract books (3). We categorized the oral presentation abstracts according to study design (prospective, retrospective), in which institution the study is done (university hospital, training and research hospital, or others), and whether there was a thesis study. Studies in which the preparations were re-evaluated and studies in the form of file scanning were evaluated as retrospective studies. The case series, reviews, and survey studies were also evaluated as retrospective studies. Evaluations made by taking new sections from paraffin blocks, experimental studies, studies using a new immunohistochemical and histochemical stain, molecular studies using new sections were evaluated as prospective studies. The private hospitals and laboratories and second step government hospitals are grouped as other institutions.

We searched the national thesis center with the name and authors of the study to see if the presented study was a publication produced from the thesis of the specialty in medicine (4). Then, we used the electronic search database Google Scholar (Google Inc., Mountain View, CA, USA) to analyze whether an abstract was published as a full-text in a scientific journal. After the finding published articles, the article's full title and all author's (starting from the first author) were searched in PubMed (National Library of Medicine, Bethesda, MD, USA), and TUBITAK ULAKBIM (Cahit Arf Information Center, Ankara, Turkey) databases and cross-checked and confirmed that it was the final publication (5-7).

The publication rates of oral presentations by years were calculated, and all published presentations were analyzed in terms of peer-reviewed journal type. Journals in which abstracts were published were grouped according to their indexing in the Master Journal List (Thomson Reuters, NY, USA) and TUBITAK ULAKBIM (Cahit Arf Bilgi Merkezi, Ankara, Turkey) databases. These journals were divided into three groups as SCI(E) and out of the scope of SCI(E) international peer-reviewed journals and national peer-reviewed journals according to their indexing defined in the master journal list and Turkish medical index.

The time between presentation and publication was also analyzed.

The abstract presented and the last published article were compared to assess any discrepancies such as the title of the study, author names, number, order, and material method. The article was deemed to have been published if it contained at least one common hypothesis, study design, or conclusion and had one co-author (presenter or first author). However, studies with different sample sizes and/or using extra material/methods were not included. We chose the online publication dates of the articles for analyzing the publication time in our study, if not, the publication dates in the relevant journal as data.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA).

The publication time of oral presentations was given with the median, minimum, and maximum. The numbers and frequencies of oral presentations according to years, institutions, and study design, whether they are thesis studies and whether they are published or not, and the number and frequencies of the published abstracts according to years, institutions, study design, whether they are thesis studies and the journals in which they are indexed, were evaluated with descriptive statistics. Comparison of publication rates and indexing journals were evaluated using the chi-square analysis due to congress year, institutions type, thesis study, and study design. The Chi-square test or Fisher-Freeman-Halton Exact test (when chi-square test assumptions do not hold due to low due to low expected cell counts), where appropriate, was used to compare. The parameters with more than two variables were grouped as two in sequence and turned into tables with four compartments. The statistical difference between these new groups was analyzed with the chi-square test and the parameter that made a significant difference was determined. As the publication time was not normally distributed the Kruskal-Wallis test were conducted to compare this parameter and institutions, congress year, and indexing. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. A p-value of <0.05 was considered statistically significant with a 95% confidence interval (CI).

RESULTS

Between 2014 and 2018, 378 studies were presented orally at national pathology congresses. The distribution of the presentations according to these years are 30 (7.9%), 60 (15.9%) 64 (16.9%) 74 (19.6%) and 150 (39.7%), respectively. In the 5-year analysis, the total number of abstracts accepted for presentation at congresses were 879, 1002, 687, 728 and 771, respectively, by years. 3.41% (n=30) of the abstracts in 2014, 5.89% (n=60) in 2015, 9.31% (n=64) in 2016, 10.16% in 2017 (n=74) and 19.45% (n=150) in 2018 were orally presented. 199 (52.6%) of the presentations were designed prospective and 179 (47.4%) were retrospective studies. Of the retrospective studies, 0.03% (n=6) were survey studies, 0.05% (n=10) case series, and 0.027% (n=5) case reports. In addition, 64 (16.9%) of these abstracts are studies obtained from specialty theses in medicine. Of the institutions where the studies were conducted, 278 (73.5%) were university hospitals, 89 (23.5%) were training and research hospitals, and 11 (3.0%) were other institutions (**Table 1**).

There was no statistically significant difference in the rate of publication of abstracts among the institutions (p=0.127). There was no statistically significant difference between the publication rate of the abstract and whether it was a thesis study or not (p=0.822). The publication rate of the studies presented at the 2018 national pathology congress was found to be significantly lower than in other years (p=0.001). In addition, the publication rate was found to be significantly higher in the prospective design of the study than in the retrospective (p=0.031) (**Table 2**).

The average publication time of the oral abstracts presented was 15.0±12.3 (0.1-68.9) months. When the publication times of these abstracts were examined, it was found that there was no significant difference between the institution where the study was conducted, the study design, the congress year in which it was presented, and the journals indexed (p=0.424, p=0.132, p=0.324, and p=0.320 respectively). However, the publication time of the abstracts obtained from thesis studies was significantly longer compared to non-thesis studies (p=0.004) (**Table 3**).

Table 1. Baseline characteristics of orally presented abstracts

The congress year	Presented abstracts	Institution			Study design		Thesis study	Publication rate
		University	Research and training hospital	Other	Prospective	Retrospective		
	n (% total)	n (% per year)						
2014	30 (7.9)	23 (76.7)	7 (23.3)	0 (0)	22 (73.3)	8 (26.7)	3 (10.0)	16 (53.3)
2015	60 (15.9)	39 (65.9)	17 (28.3)	4 (6.7)	33 (55.0)	27 (45.0)	12 (20.0)	20 (33.3)
2016	64 (16.9)	48 (75.0)	15 (23.4)	1 (1.6)	33 (51.6)	31 (48.4)	12 (18.8)	17 (26.6)
2017	74 (19.6)	59 (79.7)	13 (17.6)	2 (2.7)	48 (64.9)	26 (35.1)	16 (21.6)	24 (32.4)
2018	150 (39.7)	109 (72.6)	37 (24.7)	4 (2.7)	63 (42.0)	87 (58.0)	21 (14.0)	25 (16.7)
Total	378 (100)	278 (73.5)	89 (23.5)	11 (3.0)	199 (52.6)	179 (47.4)	64 (16.9)	102 (27.0)

Table 2. Publication rates of orally presented abstracts

	Published n (%)		p value
	Yes	No	
The congress year			0.83[a]
2014	16 (53.3)	14 (46.7)	
2015	20 (33.3)	40 (66.7)	
2016	17 (26.6)	47 (73.4)	
2017	24 (32.4)	50 (67.6)	0.001[a*]
2018	25 (16.7)	125 (83.3)	
Institution			0.127[b]
University	71 (25.5)	207 (74.5)	
Research and training hospital	30 (33.7)	59 (66.3)	
Other	1 (9.1)	10 (90.9)	
Thesis Study			0.822[a]
Yes	18 (28.1)	46 (71.9)	
No	84 (26.8)	230 (73.2)	
Study design			0.031[a*]
Prospective	63 (31.7)	136 (68.3)	
Retrospective	39 (21.8)	(78.2)	

[a]p-value's calculated by chi-square analysis, [b]p-value's calculated by Fisher-Freeman-Halton Exact test, *Significantly different values

Table 3. Publication time of orally presented abstracts

	Publication time (month)	p value
	Median (Min – Max)	
Institution		0.424[c]
University	13.8 (0.1–68.9)	
Research and training hospital	11.6 (0.2–58.3)	
Other	26.6 (26.6–26.6)	
Thesis study		0.004[d*]
Yes	20.3 (8.5–43.5)	
No	11.4 (0.1–68.9)	
Study design		0.132[d]
Prospective	14.5 (0.1–68.9)	
Retrospective	10.8 (0.2–40.4)	
The congress year		0.324[c]
2014	15.9 (0.4–68.9)	
2015	10.0 (0.1–58.3)	
2016	15.4 (0.3–40.4)	
2017	14.0 (1.6–36.2)	
2018	10.8 (0.2–26.6)	
Indexing		0.320[c]
SCI(E)	12.9 (0.2–68.9)	
IPRJ	9.3 (0.1–29.8)	
NJ	16.0 (0.9–58.3)	

[c]p-value's calculated by the Kruskal-Wallis analysis, [d]p-value's calculated by the Mann Whitney U analysis, *Significantly different values, SCI(E): Science citiation index (expanded), IPRJ: out of the scope of SCI(E) international peer-reviewed journals, NJ: National peer-review journal

When the indexing of the journals in which the abstracts were published was evaluated, it was seen that the congress where the study was presented with the institution did not make a significant difference (p=0.314). In addition, it was found that prospectively designed studies were significantly more published in SCI (E) indexed journals than retrospective studies (p=0.02) (**Table 4**).

Table 4. Indexing of published abstracts

	Indexing n (%)			p value
	SCI	IPRJ	NJ	
Institution				0.314[a]
University	45 (63.4)	13 (18.3)	13 (18.3)	
Research and training hospital	18 (60.0)	5 (16.7)	7 (23.3)	
Other	0 (0.0)	1 (100.0)	0 (0.0)	
Thesis study				0.077[a]
Yes	7 (38.9)	6 (33.3)	5 (27.8)	
No	56 (66.6)	13 (15.5)	15 (17.9)	
Study design				0.02[a]*
Prospective	44 (69.8)	12 (19.1)	7 (11.1)	
Retrospective	19 (48.8)	7 (17.9)	13 (33.3)	
The congress year				0.275[a]
2014	13 (81.2)	1 (6.3)	2 (12.5)	
2015	13 (65.0)	4 (20.0)	3 (15.0)	
2016	13 (76.4)	2 (11.8)	2 (11.8)	
2017	13 (54.1)	4 (16.7)	7 (29.2)	
2018	63 (61.8)	19 (18.6)	20 (19.6)	

[a]p-value's calculated by chi-square analysis, *Significantly different values, SCI(E): Science citation index (expanded), IPRJ: out of the scope of SCI(E) international peer-reviewed journals, NJ: National peer-review journal

DISCUSSION

Our study is the first study of the publication rate of oral presentations presented at the national pathology congresses in Turkey. In national pathology congresses, as in other congresses, abstracts are evaluated in a detailed scoring system. Abstracts that do not meet the criteria for being an oral presentation are either accepted as poster presentations or rejected. It is considered that these papers, which are examined and selected, are highly likely to be published in peer-reviewed journals (8,9).

The rate of oral presentations in the national pathology congress is increasing year by year. While this rate was 3.41% (n=30) in 2014, it increased to 19.45% (n=150) in 2018. The increase in the scientific quality of the studies is an important factor that increases the rate of acceptance of the submitted abstracts as oral presentations. In the increase of this rate, the obligation to make oral presentations at national and international scientific meetings was brought to the criteria of associate professorship determined by the higher education board, which may have led researchers to prepare better quality studies and make oral presentations.

After two years of follow-up, 27% of the abstracts presented in the national pathology congresses held consecutively between 2014-2018 were published in a peer-reviewed journal. This rate is lower than other international pathology congresses and congresses in other branches. In the study conducted by Song et al., the publication rate of the abstracts presented in USCAP was found to be 36% and it was stated that the average was between 30-50%. In this study, the publication rates of the poster and oral presentations were examined, and the publication rate of oral presentations was found to be higher (1). The low publication rate in our study may be related to the shorter follow-up period. Considering the publication rate by year, the publication rate in 2018 (16.7%) was found to be significantly lower than in other years (Table 2). In 2014, this rate is 53.3%. We think that the lengthening of the follow-up period affects the duration of the publication.

Considering the study designs of the abstracts, 52.6% were prospective and 47.4% were retrospective studies. Case series, case reports, and questionnaire studies were included in the retrospective group.

In our study, 31.7% (n=63) of the prospectively designed studies and 21.8% (n=39) of the retrospectively designed studies were published. When evaluated according to study design, the publication rate in prospective studies was found to be significantly higher than retrospective studies (p=0.031). This can be explained by the higher publication quality of prospective studies. The fact that retrospective studies give repetitive results and that refereed journals generally give priority to articles that give comprehensive and new results may be among the factors that reduce the rate of publication. In addition, the fact that peer-reviewed journals do not receive case reports or they accept very rare and specific cases may be one of the factors that reduce the rate of publication in the retrospective group.

Considering the congress time and publication time, the average period of publication was found to be 15 months. In the study of Aksüt et al, this period was found to be 16.7 months on average, and 18.4 months in the study of Scherer et al. (9,10). The average publication time in our study is shorter than in other studies. Variables such as the differences in the evaluation stages between journals, the time waited by the referees, the difference in the number of issues published annually may affect this period. When the publication times of these abstracts were examined, it was found that there was no significant difference between the institution where the study was conducted, the study design, the congress year in which it was presented, and the journals indexed (p=0.424, p=0.132, p=0.324, and p=0.320 respectively). However, the publication time of the abstracts obtained

from thesis studies was significantly longer compared to non-thesis studies (20.6±9.5 months). While trying to adapt in the first years of the specialty, not having enough time to publish the specialty theses, the concerns caused by the inexperience in the first days of the specialization may be among the reasons that suspend the article from writing.

Considering the institutions to which the abstracts were sent in our study, although there was no statistically significant difference between the institutions, the rate of sending abstracts from university hospitals was the highest (73,5%). training and research hospitals follow with a 23.5% publication rate. In the study of Aksüt et al., the publication rate of abstracts sent from university hospitals was found to be significantly higher than other institutions (9). In the study of Oktay et al. evaluating the publication rate of abstracts presented at national cardiology congresses, the rate of publication sent from training and research hospitals was found to be higher. In their study, they associated these hospitals as specialized with experienced staff (11).

The publication rate of oral presentations made in pathology congresses in SCI(E) indexed journals was higher than in other journals. It was reported that the SCI(E) publication rate was 85.7% in Oktay et al.'s study and was 48.5% in Aksüt et al.'s study (11). In our study, this rate was found to be 62%. In addition, 19% of the publications were published in national refereed journals and 19% in other international refereed journals other than SCI(E). Although the publication of the presented study in high impact factor journals shows the high scientific quality of the congresses, it is a matter of debate whether the number of publications in international refereed journals is an indicator of scientific performance (12). To evaluate the quality of publications, factors such as the number of citations and the h index should also be considered (13). We did not evaluate the number of citations of the oral presentations published in our study and the impact factors of the journals.

Our study has some limitations. Google Scholar, PubMed, and TUBITAK ULAKBIM databases were used for scanning. For this reason, may not have been able to access the articles published in different databases. Poster presentations were not included in the study. Due to the limited number of studies on the publication rate of presentations presented in pathology congresses, sufficient comparisons could not be made.

CONCLUSION

As a result, the publication rate of oral presentations in pathology congresses is close to other congresses. To reach the same level as international congresses, we think that this ratio will increase by increasing the scientific quality of the studies. We believe that researchers should develop not only oral presentations but also encouraging methods to transform studies into publications. Giving make scientific research training during residency may contribute to increasing this rate.

ETHICAL DECLARATIONS

Ethics Committee Approval: In our study, only open access data were used, therefore, ethics committee approval was not required.

Referee Evaluation Process: Externally peer-reviewed.

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

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The effect of rehabilitation support on male and female after intertrochanteric femoral fracture treatment

Betül Başar

University of Health Sciences, Gaziosmanpaşa Training and Research Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Turkey

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ABSTRACT

Aim: The aim of our study is to investigate the effect of rehabilitation support after intertrochanteric femur fractures on men and women. The results of the groups consisting of male and female patients who received and did not receive rehabilitation support were compared both between the same sexes and between different sexes.

Material and Method: One hundred twenty four patients were evaluated under two groups according to whether they received rehabilitation support or not. First group (no rehabilitation support) consists of 42 females, and 29 males, and second group (rehabilitation support) consists of 30 females, and 23 males. While the patients in the first group performed the exercises themselves at home, the patients in the second group received rehabilitation support under the guidance of a physiotherapist. The patients in both groups were also evaluated under 2 subgroups as male and female.

Results: There was no significant differences between both groups in terms of mean age, female male ratio, fracture type, mean follow-up time, Harris hip score, Barthel life index, Parker and Palmer Mobility Scale before fracture. There was also no significant difference between the subgroups of the both groups. Harris hip score, Barthel life index, and Parker and Palmer Mobility Score of males were better than females at the final follow-up in the first group. The results of females were worse than pre-fracture, but there was no difference in males at the final follow-up. Harris hip score, Barthel life index, and Parker and Palmer Mobility Score of males were better than females at the final follow-up in the second group as first group. While the results of females were not different compared to pre-fracture, the results were better in males at the final follow-up. When the female and male subgroups of both groups were compared with each other, it was determined that the results in male and female subgroups in the 2nd group were significantly better.

Conclusion: The continuity of rehabilitation support after hospital discharge is very important. Although rehabilitation support positively affects the results in male and female, it is much more important for female than male.

Keywords: Intertrochanteric femural fracture, rehabilitation support, functional results

INTRODUCTION

Intertrochanteric femural fracture is one of the most common proximal femoral injuries in the elderly population (1). The comorbidities such as decreased bone mineral density, physical functional insufficiency, undernutrition, cognitive impairment, and vision problems increase risk of intertrochanteric femur fracture at elderly patients (2). The life expectancy of the population has increased in the last decade. Intertrochanteric femur fracture has become an important health problem with the increase in the elderly population (1).

Mortality and morbidity increase if patients remain bedridden for a long time after intertrochanteric femural fracture. Prolonged immobilization causes morbidities like pressure ulcer, urinary tract infection, and respiratory tract infection. Early mobilization and rehabilitation play an important role in preventing these complications (3).

Surgical treatment is the best option in intertrochanteric femural fracture (4). Stable fixation should be provided with the implants. The patients should be mobilized in the early postoperative period. (5). Early mobilization and rehabilitation are started under the guidance of a physiotherapist. This process does not exceed 7-10 days. While some patients do not receive rehabilitation support, some patients continue their rehabilitation under the guidance of a physiotherapist after hospital discharge.

Corresponding Author: Betül Başar, betulakarvardar@hotmail.com

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The aim of our study is to investigate the effect of rehabilitation support after intertrochanteric femur fractures on men and women. The results of the groups consisting of male and female patients who received and did not receive rehabilitation support were compared both between the same sexes and between different sexes.

MATERIAL AND METHOD

This retrospective, clinical trial was approved by the Clinical Researchs Ethics Committee of Gaziosmanpaşa Training and Research Hospital (Date: 17.03.2021, Decision No: 2021-227) and was performed in accordance with the tenets of the Declaration of Helsinki (6). All methods were performed following the relevant guidelines and regulations. After informing the patients about the possible side effects of the treatments, a written informed consent was obtained from each patient.

This study included independently living intertrochanteric femoral fracture patients, over 70 years of age, who were surgically treated in January 2014 and January 2019. The patients were operated within 10 days after injury. The exclusion criterias were inability to reach the patient, death of the patient, a history of the other side proximal femoral fracture, additional fractures, and pathologic fractures. The fracture type was evaluated according to AO classification (7). 31.A1 and 31.A2 type fractures were included in our study.

The patients included in the study were found by scanning the hospital archive, which has been kept regularly since the beginning of 2014. Patients with missing data were not evaluated. Two hundred seventy five patients were evaluated retrospectively from the hospital archive. One-hundred fifty-one patients were not included in our study. 72 patients could not be reached, 32 patients did not come to the last follow-up, 30 patients had additional fractures in their lower extremities, 12 patients had a history of proximal femur fracture on the contralateral side, and 5 patients had pathological fractures. One-hundred and twenty-four patients were included in our study. At the time of fracture, all patients were either living in their own home or in some sort of community housing comparable to their own home. They had either fully independent or partially assisted lifestyles. All patients were independently mobilized without assistive device. The patients were evaluated under two groups according to whether they received rehabilitation support under the guidance of a physiotherapist hospital discharge. Group 1 (No Rehabilitation Support) consists of 42 females, and 29 males, and group 2 (Rehabilitation Support) consists of 30 females, and 23 males. The patients were called to the hospital to perform control examinations and radiological evaluations.

Rehabilitation was initiated under the guidance of a physiotherapist on the first day after surgery for the patients in both groups. Rehabilitation continued until hospital discharge. The mean hospital discharge time was 5.39±2.70 days in group 1 and 5.58±2.69 days in group 2. Informative brochures were given to the patients at discharge for the continuity of rehabilitation. The patients in first group did not receive rehabilitation support and tried to do their exercises themselves. The patients in the 2nd group received rehabilitation support under the guidance of a physiotherapist in a nursing home or in their own homes.

All patients received the same rehabilitation support that was started at the end of 2013. This rehabilitation support was applied in the same way to all patients who were operated for hip fracture in the Orthopaedics and Traumatology service. Rehabilitation support was implemented to include the following: strengthening exercises mainly for hip flexors, extensors, abductors, and knee extensors; range-of-motion (ROM) exercises, mainly for the hip joint; balance training; functional training such as sit-to-stand training, ambulation training, and stair climbing; practice of safe and efficient transfer techniques; adjustment of walking aids; and adaptation and modification of the living area. The exercises were applied according to the individual capacity and general condition of each patient. Two times a day for 10 repetitions for each item were performed. The number of repetitions and sets was increased if the patients tolerated these exercises under the guidance of a physiotherapist. 0.5-1 kg sandbags were used as resistance according to the individual capacity of each patient. If the patients had any discomfort during rehabilitation, rehabilitation was suspended. Rehabilitation support was continued for 3 months.

The pre-fracture Harris Hip Score, Barthel Life Index, Parker and Palmer Mobility Score of the patients were calculated with the forms filled in verbally when the patients were admitted to the hospital due to the fracture. These informations were obtained from hospital records. The values at the last controls were not taken from the hospital records. The same physiotherapist calculated these scores by calling the patients for control. Fracture healing was controlled by direct radiography at final follow-up. Evaluation of the patients was made according to the Harris Hip Score for clinically, Barthel Life İndex for daily life activities and Parker and Palmer Mobility Score for mobilization by the same physiotherapist in Gaziosmanpaşa Training and Research Hospital at final follow-up (8-10).

Statistical Analysis

The data were compared using Student's unpaired t test/ Mann-Whithey test for quantitative measurements,

and Chi-square test/Fischer exact test for qualitative measurements. A p value below 0.05 was considered significant. The data were entered in MS Excel spread sheet,and statistical analysis was done using Statistical Package for Social Seciences (SPSS) version 16.0.

RESULTS

Comparison of Male and Female in Group 1 (No Rehabilitation Support)

In the pre-fracture evaluation; forty-two females for an average of 25.42±8.41 months and 29 males for a mean of 27.68±9.66 months were evaluated. There was no statistically significant difference between males and females in terms of mean age, follow-up time, and fracture type according to AO classification (p> 0.05) (**Table 1**).

The Harris hip score of females was poor in 20, moderate in 12, good in 7, and excellent in 3. Eight had poor, 12 had moderate, 7 had good, and 2 had excellent results in males. Nine patients were independent, 28 patients were minimally dependent, and 5 patients were partially dependent according to the Barthel life index in females. Six patients were independent, 22 patients were minimally dependent, and 1 patient was partially dependent in males. The mean value was 6.38±1.22 in females and 6.82±1.07 in males according to Parker and Palmer Mobility Score (**Table 1**). There was no statistically significant difference between males and females in terms of Harris hip score, Barthel life index and Parker and Palmer Mobility Scale at pre-fracture period (p>0.05), (**Table 1**).

In the last follow-up evaluation; the Harris hip score of females was poor in 38, good in 3, and excellent in 1. Sixteen had poor, 6 had moderate, 6 had good, and 1 had excellent results in males. Two patients were independent, 9 patients were minimally dependent, 22 patients were partially dependent, 8 patients were very dependent, and 1 patient were totally dependent according to the Barthel life index in females. Four patients were independent, 17 patients were minimally dependent, and 8 patient was partially dependent in males. The mean value was 5.42±1.67 in females and 6.72±0.88 in males according to Parker and Palmer Mobility Score. (Table 1). There were statistically significant differences between males and females in terms of Harris hip score, Barthel life index, and Parker and Palmer Mobility Scale at last follow-up in the first group (p<0,05), (Table 1). The result was better in males. Harris hip score, Barthel life index and Parker and Palmer Mobility Scale results in the last follow-up were compared with the pre-fracture results. The results were statistically significantly worse in females at the last follow-up (p<0.05). There was no statistically significant difference between the final follow-up results and pre-fracture results in males (P>0.05), (**Table 1**).

Comparison of Males and Females in Group 2 (Rehabilitation Support)

In the pre-fracture evaluation; the mean follow-up period was 27.60±12.06 months in females and 30.43±12.10 months in males in the second group (Rehabilitation Support). There was no statistically significant difference between males and females in terms of mean age, follow-up time, and fracture types according to AO classification (p> 0.05) (**Table 2**).

Table 1. Patient characteristics, functional scores, and mobility scores in group 1 (no rehabilitation support)

Non-rehabilitation group	Female (No:42)	Male (No:29)	P
Mean Age	76.25±4.84	77.24±4.71	0.3928
Mean Follow-up Period (month)	25.42±8.41	27.68±9.66	0.3119
AO Classification			0.6220
A1	24	19	
A2	18	10	
Operation Period (day)	5.61±2.71	5.06±2.71	0.4042
Pre-operative Harris Hip Score	70.30±11.50	74.34±10.29	0.0955
Follow-up Harris Hip Score	50.69±15.36	68.86±11.92	<0.0001
P	<0.0001	0.0737	
Pre-operative Barthel Life Index	68.69±12.10	72.58±8.19	0.0861
Follow-up Barthel Life Index	49.76±15.57	66.72±11.36	<0.0001
P	<0.0001	0.0671	
Pre-operative Parker Palmer Mobility Score	6.38±1.22	6.82±1.07	0.1194
Follow-up Parker Palmer Mobility Score	5.42±1.67	6.72±0.88	0.0007
P	0.0103	0.6320	

Table 2. Patient characteristics, functional scores, and mobility scores in group 2 (rehabilitation support)

Rehabilitation group	Female (No:30)	Male (No:23)	P
Mean age	78.23±6.09	76.60±5.75	0.3260
Mean follow-up period (month)	27.60±12.06	30.43±12.10	0.4016
AO classification			0.7750
A1	20	14	
A2	10	9	
Operation period (day)	5.40±2.94	5.82±2.38	0.5633
Pre-operative Harris hip score	72.90±13.68	71.78±14.03	0.8435
Follow-up Harris hip score	74.46±13.72	82.13±13.80	0.0381
P	0.6150	0.0108	
Pre-operative Barthel life index	71.66±15.27	70.86±12.40	0.8014
Follow-up Barthel life index	68.00±14.77	77.39±13.30	0.0173
P	0.4156	0.0429	
Pre-operative Parker Palmer mobility score	6.63±1.06	6.47±1.27	0.5401
Follow-up Parker Palmer mobility score	6.76±1.22	7.47±1.37	0.0305
P	0.4311	0.0124	

The Harris hip score of females was poor in 13, moderate in 6, good in 7, and excellent in 4. Ten had poor, 5 had moderate, 5 had good, and 3 had excellent results in males. Thirteen patients were independent, 11 patients were minimally dependent, and 6 patients were partially dependent according to the Barthel life index in females. Nine patients were independent, 12 patients were minimally dependent, and 2 patients were partially dependent in males. The mean value was 6.63±1.06 in female and 6.47±1.27 in male according to Parker and Palmer Mobility Score (**Table 2**). There was no statistically significant difference between the second group males and females in terms of Harris hip score, Barthel life index and Parker and Palmer mobility scale at pre-fracture period (p>0,05) (**Table 2**).

In the last follow-up evaluation; the Harris hip score of females was poor in 11, moderate in 8, good in 6, and excellent in 5. Three had poor, 4 had moderate, 9 had good, and 7 had excellent results in males. Thirteen patients were independent, 11 patients were minimally dependent, and 6 patients were partially dependent according to the Barthel life index in females. Nine patients were independent, 12 patients were minimally dependent, and 2 patients was partially dependent in males. The mean value was 6.76±1.22 in female and 7.47±1.37 in male according to Parker and Palmer Mobility Score (**Table 2**). There were statistically significant differences between the second group males and females in terms of Harris hip score, Barthel life index and Parker and Palmer mobility scale at last follow-up (p<0,05) (**Table 1**). Better results were obtained in males. Harris hip score, Barthel life index and Parker and Palmer mobility scale results in the final follow-up were compared with the pre-fracture results. There was no statistically significant difference between the final follow-up results and pre-fracture results in females (P>0.05), (**Table 2**). The results were statistically significantly better in males at the last follow-up (p<0.05).

Comparison of Females in Group 1 and Group 2

There was no statistically significant difference between group 1 and group 2 females in terms of mean age, follow-up time, fracture types according to AO classification, pre-fracture Harris hip score, Barthel life index and Parker and Palmer Mobility Scale (p>0.05), (**Table 3**).

Statistically significantly better results were obtained in Group 2 females in the final follow-up (p>0.05) (**Table 3**).

Comparison of Males in Group 1 and Group 2

There was no statistically significant difference between group 1 and group 2 males in terms of mean age, follow-up times, and fracture types according to AO classification, pre-fracture Harris hip score, Barthel life index and Parker and Palmer Mobility Scale (p> 0.05), (**Table 4**).

Statistically significantly better results were obtained in Group 2 males in the final follow-up. (p>0.05), (**Table 4**).

Table 3. Female patient characteristics, functional scores, and mobility scores in both group

Female	Non-rehabilitation group (No:42)	Rehabilitation group (No: 30)	P
Mean age	75.97±4.54	78.23±6.09	0.0923
Mean follow-up period (month)	25.42±8.41	27.60±12.06	0.3999
AO classification			0.4688
A1	24	20	
A2	18	10	
Operation period (day)	5.61±2.71	5.40±2.94	0.7489
Pre-operative Harris hip score	70.30±11.50	72.90±13.68	0.4646
Follow-up Harris hip score	50.69±15.36	74.46±13.72	<0.0001
Pre-operative Barthel life index	68.69±12.10	71.66±15.27	0.4137
Follow-up Barthel life index	49.76±15.57	68.00±14.77	<0.0001
Pre-operative Parker Palmer mobility score	6.38±1.22	6.63±1.06	0.4387
Follow-up Parker Palmer mobility score	5.42±1.67	6.76±1.22	0.0007

Table 4. Male patient characteristics, functional scores, and mobility scores in both group

Male	Non-rehabilitation group (No:29)	Rehabilitation group (No: 23)	P
Mean age	77.24±4.71	76.60±5.75	0.6724
Mean follow-up period (month)	27.68±9.66	30.43±12.10	0.3805
AO classification			0.7778
A1	19	14	
A2	10	9	
Operation period (day)	5.06±2.71	5.82±2.38	0.2901
Pre-operative Harris hip score	74.34±10.29	71.78±14.03	0.5430
Follow-up Harris hip score	68.86±11.92	82.13±13.80	0.0003
Pre-operative Barthel life index	72.58±8.19	70.86±12.40	0.9119
Follow-up Barthel life index	66.72±11.36	77.39±13.30	0.0017
Pre-operative Parker Palmer mobility score	6.82±1.07	6.47±1.27	0.2330
Follow-up Parker Palmer mobility score	6.72±0.88	7.47±1.37	0.0072

DISCUSSION

The life expectancy of the general population is increased significantly in the past decades. The prevalence of proximal femur fractures and particularly intertrochanteric femoral fractures increases as the quality of bone decreases with age (11).

The success of the surgical treatment and the union of the fracture after fixation are not sufficient for the successful clinical results. Rehabilitation and early mobilization are very important for clinical results. The success in the functional results is significantly related with the ambulatory ability (12). Therefore, mobilization and rehabilitation support is very important to increase the mobilization capacity in the early period (3).

The proximal femoral nail was a treatment choice for intertrochanteric femoral fracture. Rehabilitation and mobilization can be started immediately after surgery (13). Therefore, we preferred proximal nail in the surgical treatment of our patients.

Hospital-based rehabilitation positively affects functional results. However, the high cost of hospital-based rehabilitation is a problem (14). Nowadays, hospital stays are not long enough for rehabilitation due to high costs. Therefore, rehabilitation support plays an important role after hospital discharge. Post-hospital rehabilitation includes a rehabilitation facility, a skilled nursing facility, and home-based physical therapy (15). There was no significant difference between hospital-based therapy and home-based therapy at 12-month follow-up. Only hospital-based therapy gives better results in terms of upper extremity motor strength (16).

Functional results were better in patients who received rehabilitation support in the study of Lahtinen et al. (14). Functional outcomes are expected to be better in arthroplasty than in osteosynthesis with intramedullary nail or plate screws (17). The results of males and females were not compared in these studies (14).

The effect of rehabilitation on hip fracture was evaluated in a study conducted by Lieberman et al. However, the study included a heterogeneous patient group with different hip fractures and different treatment options. While arthroplasty was applied to some of the patients, osteosynthesis was applied to the others. No research has been conducted on patients who do not receive rehabilitation support (18).

Magazine et al. compared two different rehabilitation support after hip fracture. A homogeneous patient group was also not included in this study. The patients with different hip fractures and different treatment options were included in the study. The effect of gender on the results has not been studied. It was determined that the effect of two different rehabilitation supports on the results was not different (19).

The patients were not evaluated in homogeneous groups in these studies investigating the effect of rehabilitation on hip fractures. Our study was conducted on a homogeneous group. There is no study in the literature on the effect of rehabilitation in patients who underwent proximal nailing for intertrochanteric femoral fractures. We compared the results of patients who received rehabilitation support and those who did not, and the effect of whether there was rehabilitation support in male and female patients.

CONCLUSION

It was found that rehabilitation support affects the results positively in intertrochanteric femoral fractures fixed with a proximal femoral nail in our study. Although rehabilitation support was not applied in males, it was determined that pre-fracture functional values were reached in the final follow-up. Pre-fracture functional results could not be achieved in females who did not receive rehabilitation support at the final follow-up. Lack of rehabilitation support negatively affects outcomes in females. On the other hand, the results were much better than before fractures in males who received rehabilitation support. Rehabilitation support is very important for both females and males. Even if rehabilitation is not applied to male patients, they regain their previous functional capacity. If post-surgical rehabilitation is not applied, the results are much worse in females. Therefore, rehabilitation should be applied after surgical treatment of intertrochanteric femoral fractures especially in females.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Clinical Researchs Ethics Committee of Gaziosmanpaşa Training and Research Hospital (Date: 17.03.2021, Decision No: 2021-227).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Alteration of cerebral perfusion and cortical thickness in depression episodes: a comparative MRI study

Özkan Kılınç[1], Mustafa Hızal[1], Özden Arısoy[2], Nur Özgedik[2], Oya Kalaycıoğlu[3]

[1]Abant İzzet Baysal University, Faculty of Medicine, Department of Radiology, Bolu, Turkey
[2]Abant İzzet Baysal University, Faculty of Medicine, Department of Psychiatry, Bolu, Turkey
[3]Abant İzzet Baysal University, Faculty of Economics and Administrative Sciences, Department of Econometrics, Bolu, Turkey

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ABSTRACT

Aim: We aimed to determine the difference between cerebral perfusion and cortical thickness between first attack and recurrent in major depression patients.

Material and Method: Our study was conducted prospectively between 01.03.2017-03.03.2018 in İzzet Baysal University Department of Psychiatry. 40 patients (21 first episodes and 19 recurrent episodes) diagnosed with depression according to DSM 5 by the American Psychiatric Association and a control group of 16 healthy individuals were evaluated for cerebral blood flow and cortical thickness with Perfusion MRI. Patients were also evaluated by Hamilton depression rating scale.

Findings: The cortical thickness was significantly decreased in recurrent attacks.There was no significant difference of CBF in first episode and recurrent episodes, except cingulate cortex, which showed significantly reduced CBF values in recurrent group. In patients with higher Hamilton depression scale points, the CBF values of insular cortex were decreased.

Conclusion: These findings suggests that cortical atrophy and activation of default mode network in recurrent episodes which leads to decreased response to treatment.

Keywords: Depression, cerebral perfusion, cortical thickness, MRI

INTRODUCTION

Major depression (MD) is a common and episodic disorder, which often causes a significant functional loss and even death due to suicide (1,2). It is possible to improve the quality of life of MD patients with a correct diagnosis and treatment. There are many neuroimaging studies evaluating the pathophysiological process of depression using different imaging modalities (3-5). Positron emission tomography (PET), single photon emission computed tomography (SPECT), computed tomography (CT) angiography and perfusion magnetic resonance imaging (MRI) were often used to evaluate cerebral blood flow (6,7) and some of these reports showed alterations in both the cerebral blood flow and cortical thickness in MD patients compared to healthy controls (HC) (8-10). The decrease in cortical thickness and limbic system volume was found to be associatied with the number of the depression episodes in some of these reports (10-12). Decreased blood flow to cerebral cortical regions, such as frontal, cingulate and thalamic cortices, were reported to be associated with depression and increased episode rate (13-15). The purpose of this study was to determine whether there was a difference in cerebral blood flow and cortical thickness between the first and recurrent depressive episode patients compared to healthy controls.

MATERIAL AND METHOD

The study was carried out with the permission of Clinical Researches Ethics Committee of Bolu Abant İzzet Baysal University (Date: 09.03.2017, Decision No: 2017/31). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

40 major depression patients who applied to psychiatry clinic of our hospital between 01.03.2017-01.03.2018 were enrolled in the study and diagnosed with a semi-structured clinical interview (SCID-I) according to DSM-IV criteria by an expert psychiatrist of at least 4

Corresponding Author: Mustafa Hızal, hizal.mustafa@gmail.com
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years of experience. 21 of these patients were in their first depressive episode and 19 of them had recurrent depressive episodes. Patients under antidepressant treatment, with a diagnosis of psychiatric disorder other than major depression, with a poor cognitive performance, with a sleep disorder, with a history of alcohol and drug abuse, with a diagnosis of other medical disorders which might affect cerebral blood flow or cortical thickness (infections, neoplasms, traumatic brain injury, demyelinating diseases, hypertension, stroke, vasculitis, diabetes mellitus), with a contradiction to MRI scanning (pacemaker, MRI incompatible implants, claustrophobia, physical deformation which do not allow patient to get into MRI device), and patients below 18 or above 60 years of age were excluded from the study. The control group consisted of 16 healthy subjects with the same exclusion criteria. Depression severity of the patients and controls were evaluated with Hamilton Depression Rating Scale (HDRS).

Image Acquisition and Data Analysis

Imaging was made in a 1.5 Tesla MRI machine (Symphony; Siemens Medical Systems, Erlangen, Germany). A head and/or neck surface coil was used. Participants in first, recurrent episode and control groups underwent MRI to obtain isovolumetric 3D T1 MPRAGE on sagittal plane (TR: 2400, TE: 3.61, FOV: 240x100, slice thickness: 1.2 mm) prior to contrast medium administration. After the contrast medium (Gadovist 15 ml, 01. mmol/kg, injection rate 3 ml/sn prior to 20 ml SF push), GE T2* DSC perfusion sequence (TR:2410, TE: 47, FOV: 230x100, slice thickness 5 mm) was obtained. MR images of patients were uploaded to a workstation (syngoMMWP VE25A, Siemens AG, Berlin and Munich, Germany) for evaluations and measurements.

The thickness of bilateral prefrontal, insular, parahippocampal and cingulate cortices were measured using the T1 MPRAGE images on the axial plane. rCBF values of the same regions were measured in the axial plane of rCBF map generated in the workstation with a region of interest smaller than 1.5 cm2. A radiologist with at least 5 years of experience made the radiologic evaluation.

Statistical Analysis

The normality of rCBF and cortical thickness measurements for each location in different groups was tested with the Shapiro-Wilk normality test. Normally distributed rCBF and cortical thickness data were compared with one way ANOVA test and posthoc comparisons were done using Bonferroni correction. Non-normal distributed data were compared with Kruskal Wallis ANOVA test.

According to normal distribution, either Mann Whitney U test or student t test was used to compare the data between the two groups. The relation between rCBF, cortical thickness, depression severity, number of depressive episodes was analyzed with Pearson correlation analysis. Statistical significance was accepted as 0.05 in all statistical tests. The differences between the groups were also summarized with boxplots.

RESULT

There was no significant difference in the cortical thickness and rCBF values between the right and left hemispheres for all locations. The mean rCBF value in the right and left parahippocampal cortex were 9.9 ml/min and 9.8 ml/min in HC's; 12.9 ml/min and 13.1 ml/min the first episode group and 14.2 and 15.0 ml/min in the recurrent episode group. The mean rCBF value in the right and left prefrontal cortex were 13.8 ml/min and 13.7 ml/min in HC's; 22.0 ml/min and 25.1 ml/min in the first episode group and 17.5 ml/min and 17.9 ml/min in the recurrent episode group. The mean rCBF values in the right and left insular cortex were 12.6 ml/min and 12.7 ml/min in HC's; 22.8 ml/min and 21.6 ml/min in the first episode group and 19.6 ml/min and 18.6 ml/min in the recurrent episode group. The mean rCBF values in the right and left cingulate cortex were 10.0 ml/min and 8.5 ml/min in HC's; 21.2 ml/min and 21.6 ml/min in the first episode group and 13.6 ml/min and 13.7 ml/min in the recurrent episode group. The control group had the lowest rCBF values for each location.

The mean rCBF of the parahippocampal area was lower than the other regions in the first episode group ($p < 0.05$). The lowest mean rCBF was in the parahippocampal area (13.04±6.17) and the highest mean rCBF was in the prefrontal cortex (23.60±13.60) in the first episode group. When the locations were compared in pairs, rCBF measurements in the parahippocampal cortex in the first episode group was found to be lower than the measurements in the prefrontal cortex and insular cortex locations (p values, 0.003 and 0.002, respectively).

In the recurrent episode group, the lowest mean rCBF value was in the cingulate cortex (13.67±5.18); while the highest mean rCBF value was in the insular cortex (19.13±7.65) but, there was no significant difference between the mean rCBF values of the different locations in the recurrent episode group ($p=0.059$).

When the mean rCBF values of the first episode group was compared with the recurrent episode group, the mean rCBF values were lower in the prefrontal, cingular and insular cortices in the recurrent episode group compared to the first episode group but, a significant difference was found only in the cingulate cortex region ($p<0.05$) (**Figure 1**).

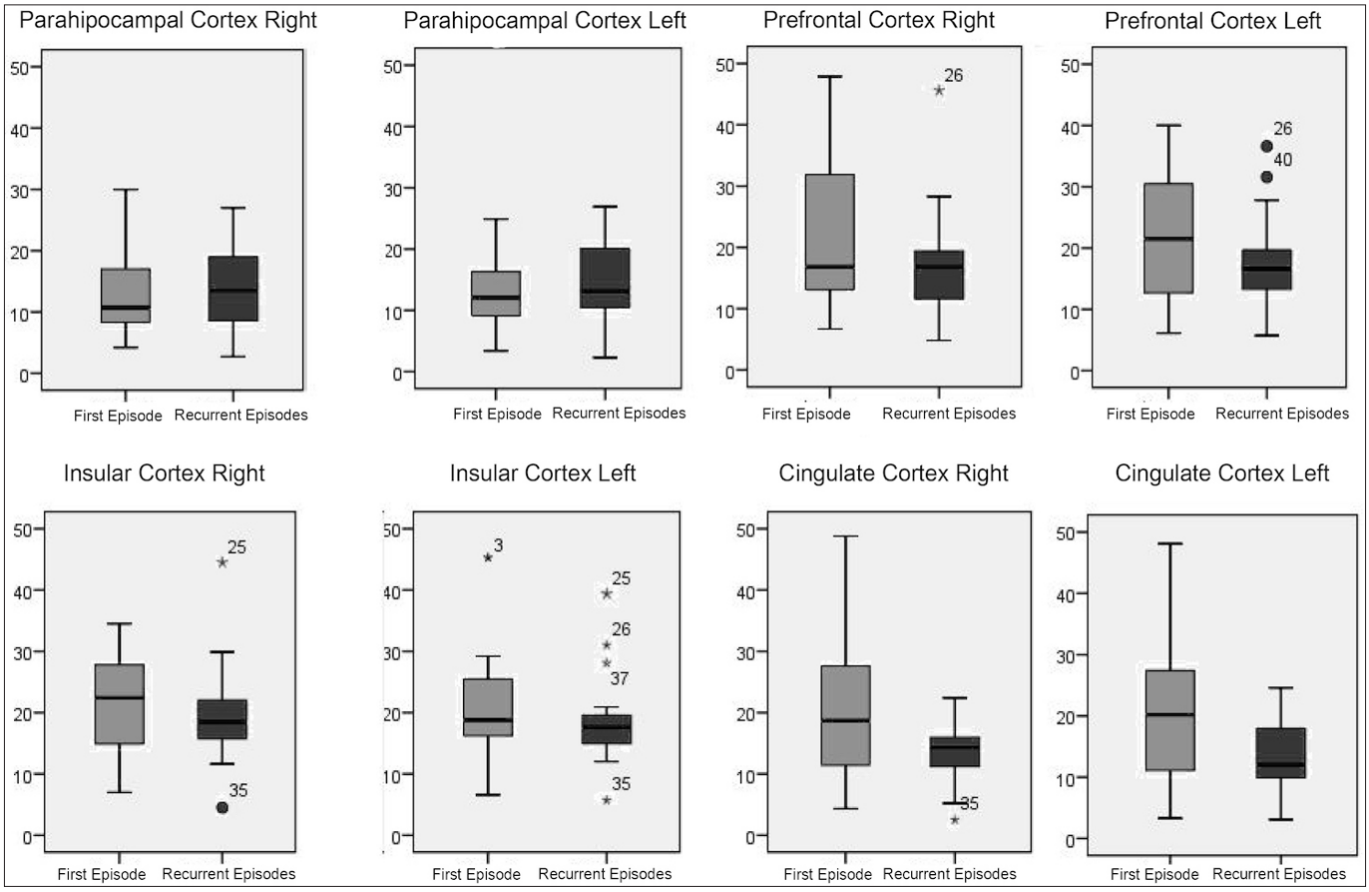

Figure 1. Comparing box plots of mean rCBF values of each location in first and recurrent episode groups. Note: regional cerebral blood flow (rCBF) value is expressed in ml/min.

In the first episode patient group, there was a significant positive correlation between rCBF value of the right prefrontal cortex and the Hamilton depression scale score ($p < 0.05$). In the recurrent depression group, a significant negative correlation was found between rCBF value of the left insular cortex and the Hamilton depression scale score ($p=0.040$) (**Table 1**).

Table 1. rCBF values of the healthy control, first episode and recurrent episode groups

Region	Healthy control	First episode group	Recurrent episode group	p
Parahippocampus				
Right	9.90±5.92	12.91±7.06	14.24±7.01	0.144
Left	9.81±5.41	13.17±5.95	15.096.66	0.081
Mean	9.86±5.60	13.04±6.17	14.67±6.43	0.096
Prefrontal cortex				
Right	13.86±89.7[a]	22.05±12.26[a]	17.52±8.90	0.027*
Left	13.71±7.45[a]	25.15±15.70[ab]	17.95±7.55[b]	0.002*
Mean	13.79±80.40[a]	23.60±13.60[a]	17.74±8.09	0.006*
Insula				
Right	12.61±8.53[a]	23.87±14.00[a]	19.64±8.24	0.007*
Left	12.78±8.50[a]	21.58±11.32[a]	18.62±7.49	0.017*
Mean	12.70±8.41[a]	22.72±12.56[a]	19.13±7.65	0.009*
Cingulate cortex				
Right	10.02±7.00[a]	21.20±12.50[ab]	13.62±5.03[b]	<0.001*
Left	8.47±5.69[a]	21.60±11.90[ab]	13.73±5.93[b]	<0.001*
Mean	9.38±6.28[a]	21.39±12.60[ab]	13.67±5.18[b]	<0.001*

Values are means (standart deviation), regional cerebral blood flow (rCBF) value is expressed in ml/min, p values obtained from One-way ANOVA test , *p significant at α<0.05. [a],[b]Same superscript letter indicates statistically significant difference in the post-hoc comparison between groups.

There were no significant differences between the cortical thickness of all localizations in the first episode group and the control group ($p>0.05$) (**Table 2**). However, the cortical thickness of all localizations of the recurrent episode group was significantly lower than both the first episode group and the control group ($p<0.05$) (**Figure 2**).

Table 2. Correlation between rCBF measurements of different locations and Hamilton depression rating scale score of the first episode and recurrent episode patient groups

Location	First Episode Group (n:21)		Recurrent Episode Group (n:19)	
	r	p	r	p
Right Parahippocampal	0.345	0.125	-0.244	0.314
Left Parahippocampal	0.247	0.280	-0.176	0.470
Right Prefrontal	0.434*	0.0049	-0.113	0.646
Left Prefrontal	0.361	0.108	-0.046	0.853
Right Insular	0.325	0.151	-0.423	0.072
Left Insular	0.331	0.143	-0.474*	0.040
Right Cingulate	0.248	0.279	-0.074	0.762
Left Cingulate	0.123	0.596	-0.062	0.802

Pearson's correlation analysis, * correlation coefficients significant at α=0.05.

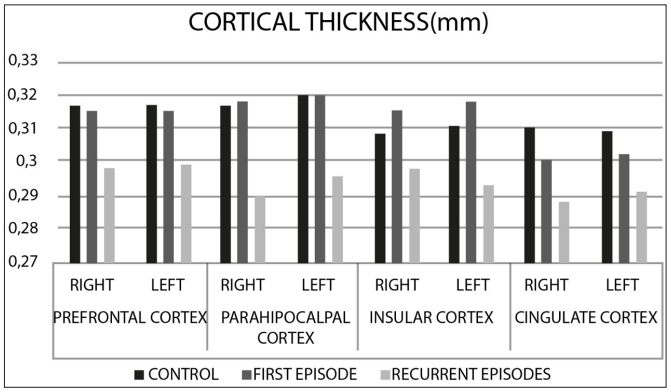

Figure 2. Mean cortical thickness values of the locations in each group. Note: Value of cortical thickness is expressed in mm.

Table 3. Comparison of the cortical thickness values of the groups

Location	Groups	Mean cortical thickness (mm)	p value
Right Parahippocampal	Control	0.318	0.003*
	First episode	0.317	
	Recurrent episode	0.290	
Left Parahippocampal	Control	0.320	<0.001*
	First episode	0.319	
	Recurrent episode	0.297	
Right Prefrontal	Control	0.317	0.010*
	First episode	0.314	
	Recurrent episode	0.298	
Left Prefrontal	Control	0.318	0.010*
	First episode	0.314	
	Recurrent episode	0.299	
Right Insular	Control	0.309	0.028*
	First episode	0.316	
	Recurrent episode	0.298	
Left Insular	Control	0.311	0.002*
	First episode	0.317	
	Recurrent episode	0.294	
Right Cingulate	Control	0.311	0.008*
	First episode	0.299	
	Recurrent episode	0.288	
Left Cingulate	Control	0.309	0.025*
	First episode	0.300	
	Recurrent episode	0.293	

p values obtained from ANOVA test, * p significant at $\alpha \leq 0.05$, cortical thickness value is expressed in mm's.

DISCUSSION

The mean rCBF value of the cingulate cortex was found to be significantly lower in the recurrent episode group compared to the first episode group and the cortical thickness were found to be significantly lower in all locations in the recurrent episode group compared to both first episode group and the control group.

There are studies that report a decrease in volume in certain cerebral regions in patients with depression. It was reported that there was a decreased right and left hippocampal volume in recurrent depressive patients (8). It was also stated that there were structural changes in the hippocampus at the first episode, however there was no change in the volume. They additionally stated that the volume loss was added to this shape disorder with recurrent episodes (10,11). Those reports were consistent with the results of this study, which showed significantly decreased thickness in the parahippocampal cortices in the recurrent episode group compared to control and first episode groups. Less hippocampal shrinkage was reported in patients responding to treatment (12).

Structural MRI studies in patients with depression were reviewed and it was reported that shrinkage in the prefrontal, anterior cingulate and orbitofrontal cortex was greater than the hippocampus in two different studies. These findings suggest that frontal and cingulate cortex may play a role as hippocampus in the pathophysiology of depression (16,17). Volume reductions were detected in subcortical structures and cortical brain structures, such as the anterior cingulate cortex and the prefrontal cortex, which have an important role in cognitive function (18). It was reported that the frontal lobe was 7.2% smaller in patients with depression than in healthy controls (9). We also detected a reduction in cortical thickness in prefrontal, cingulate and insular cortex in recurrent episode group in comparison to the remaining two groups. There are also studies reporting that volume loss in depression-related structures may be hereditary; however, further studies on this subject are necessary (19,20).

Cortical thinning is thought to occur with recurrent episodes due to intermittent and continuous changes in rCBF values. Excessive activity of the limbic system, which plays an active role in anxiety and depression, might induce hypothalamic-pituitary-adrenal axis, which in turn might cause an increase in glucocorticoid release and a decrease in volume (21-23). In addition, depression and chronic stress might cause an increase in proinflammatory cytokines leading to a decrease in serotonergic transmission and a reduction in brain-derived-neurotrophic factor synthesis through the activation of hypothalamic-pituitary adrenal axis which results in neuronal apoptosis and glial damage (24). It was reported that frontal hypoperfusion was due to a decrease in glutamate, glutamine and gamma aminobutyric acid levels and this resulted in a decrease in frontal neuronal size and glial cell density (14). Emotion blunting in depression was associated with a decrease in frontal neuronal size and glial cell density due to hypoperfusion and with treatment, an improvement was seen in these hypoperfused areas (25-28).

In previous studies, it was reported that neurochemical impairment due to hypoperfusion was effective in the development of depression (29-33). A decrease of rCBF primarily in the left hemisphere, specifically

in the left temporal lobe, left prefrontal cortex and left anterior cingulate cortex was reported in patients with depression compared to healthy individuals (4,13,21,29). It was also reported decreased cortical perfusion in bilateral frontal regions and bilateral thalamic regions in patients with refractory depressive disorder (RDB) and in the left prefrontal cortex in patients with non-refractory depressive (NRD) disorder (14). Decreased blood flow in the cingulate cortex leads to a deterioration in the regulation of emotion and a decrease in patient motivation and an increase in depression. It may also lead to an increased number of recurrent episodes (15). In our study, there was also significant reduction in rCBF value of the cingulate cortex in the recurrent group compared to the first episode group. Probably this decreased blood flow might cause a loss of function of the cingulate cortex and thus contribute to the formation of depressive symptoms through emotion dysregulation.

Also, a significant positive correlation between right prefrontal cortex rCBF value and total depression score was found in the first episode patient group. Predominantly increased rCBF in the right hemisphere, specifically in the right cerebellum, thalamus, frontal lobe and anterior cingulate cortex in depressed patients compared to healthy controls was reported in previous studies (3,21). Right hemisphere is mostly responsible for processing negative emotions and it was shown to be activated by negative facial cues (34). So, in more severely depressed patients a greater right prefrontal cortex activity might be seen as in our study. But besides that, blood flow might be increased in the right prefrontal cortex in order to protect neurons in the first episode group.

In addition, there was a significant negative correlation between rCBF value of the left insular cortex and total depression score in the recurrent depressive patients. Anterior insula and the cingulate cortex is part of the salince network (SN) and it is an internal hub mediating the interactions between central executive network (CEN) and default mode network (DMN) (35). It plays an active role in activating CEN and deactivating DMN (36). DMN is activated during tasks involving autobiographical-episodic memory, self-referential processes including self-monitoring and social cognitive processes related to self and others. The decreased blood flow to insula might cause an activation of the DMN resulting in overthinking about self, past relations and events with others in recurrent depressed patients. If this remembering and rumination is about mostly negative events this might cause an increase in depressive symptoms. In addition, decreased activity in insula might cause a deactivation of the CEN which is mostly involved in working memory, judgement and decision making in the context of goal-directed behavior. Thus, deactivation of CEN might result in a deterioration in the above mentioned cognitive functions.

In our study, rCBF values of bilateral cingulate cortex and insula and bilateral cingulate and insular cortical thickness were significantly decreased in recurrent attack patients. Because of the decrease in the blood flow and thickness of the insular and cingulate cortex, the DMN might remain active and the excitations might not be able to be forwarded to CEN, which might lead to a decreased production of appropriate behavioral responses to salient stimuli and an increase in ruminative thoughts about the past so that the effects of depression may become more resistant and severe. In addition, the decreased cortical thickness of the prefrontal and parahippocampal cortices and the decreased rCBF in the right prefrontal cortex in the recurrent episode patient group is consistent with the fact that cognitive functions, especially executive functions related to prefrontal activity and memory related to parahippocampal activity, can be more impaired in patients with recurrent attacks.

The main limitation in our study was the small number of patients. Apart from the depression in the patients, the exact distinctions of the pathologies that disrupted the brain flow could not be made and they were excluded according to the anamnesis of the patients. Since our study was cross-sectional, it was not possible to determine whether patients with first episode would be re-attacked in the following period and blood flows and cortical thicknesses could not be followed-up prospectively.

CONCLUSION

As a result, our findings showed that the cortical thickness decreased significantly in the recurrent episode group although it was not different in the first episode group compared to healthy controls, suggesting that prevention of recurrence of depression is a must in order to preserve brain health. The lower rCBF values in the bilateral cingulate cortex in the recurrent episode patients compared to first episode patients and the negative correlation between the left insular cortex CBF values and depression score in the recurrent episode group might suggest that the salience network which regulate the dynamic interactions between the large scale networks of DMN and CEN seem to be affected by depression episodes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Researches Ethics Committee of Bolu Abant İzzet Baysal University (Date: 09.03.2017, Decision No: 2017/31).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Real-life data of patients with hypoparathyroidism: a case-control study

Vedat Tan[1], Alpaslan Kemal Tuzcu[2], Zafer Pekkolay[2]

[1]Dicle University Faculty of Medicine, Department of Internal Medicine, Diyarbakır, Turkey
[2]Dicle University Faculty of Medicine, Department of Endocrinology, Diyarbakır, Turkey

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ABSTRACT

Objective: This study aims to investigate real-life data of patients with hypoparathyroidism.

Material and Method: This retrospective case-control study was carried out in a tertiary endocrine center between 1 January 2010 and 31 December 2019. Patients with a confirmed diagnosis of persistent hypoparathyroidism and healthy controls were included. Demographic characteristics of the patients, laboratory findings, etiologies of hypoparathyroidism, treatments they received, reasons for hospitalization, and complications were investigated.

Results: Sixty-five patients (mean age 42.80±13.4 years, 91% female) with hypoparathyroidism, and 54 healthy controls (mean age 33.58±11.9 years, 65% female) were included. Mean calcium level 7.95±0.92 mg/dl, and mean PTH level 9.99±6.30 pg/ml in hypoparathyroidism. Regarding the etiology of HypoPT, 51 (78%) patients had hypoPT due to surgery; 14 (22%) patients developed HypoPT due to non-surgical causes. In patients with hypoPT who underwent surgery, the mean calcium value was 8.03±0.93 mg/dl; the mean calcium value in patients with non-surgical HypoPT was 7.67±0.85 mg/dl. The mean PTH levels in non-surgical group, other group 10.16±6.21 pg/ml and 9.36±6.82 pg/ml, respectively. The most common surgery was due to multinodular goiter (72%). In 46 percent, the most common treatment was calcitriol 0.5 mcg/day and calcium 2000 mg/day. Nearly half of the patients had treatment non-compliance (46%). Eighteen percent of patients had kidney stones. Forty-three percent of the patients had been hospitalized in the last year. The most common reason for the hospitalization of patients with hypoparathyroidism was hypocalcemia, and the most common reason for this was treatment non-compliance.

Conclusion: In our study, the most common cause of hypoparathyroidism is surgery due to multinodular goiter. The most common reason for hospitalization is treatment non-compliance. Up to one-fifth of patients had kidney stones.

Keywords: Hypoparathyroidism, real-life data, hypocalcemia

INTRODUCTION

Hypoparathyroidism (HypoPT) is a rare disease characterized by low/normal parathyroid hormone (PTH) concentration despite low calcium and increased phosphorus levels (1). The most common cause of hypoPT is unintentional removal or damage to the parathyroid glands during head/neck surgery. Non-surgical hypoPT accounts for 25 percent of all patients. Although the etiology in these patients is autoimmune, infiltrative diseases, and genetic causes, most patients are idiopathic hypoPT (2-4).

Classical laboratory findings hypoPT are hypocalcemia, hyperphosphatemia, low PTH, and hypercalciuria. Symptoms of hypoPT result from neuromuscular irritability caused by hypocalcemia and include tingling, muscle cramps, and seizures. Hypocalcemia has life-threatening acute complications such as laryngospasm, seizures and cardiac arrhythmias. It has chronic complications such as cerebral calcification and kidney stones (5-7).

Conventional treatment includes orally active vitamin D and calcium. However, this treatment cannot fully fulfill the role of PTH and causes first short-term problems (such as hypocalcemia, hypercalcemia, and increased urinary calcium excretion) and then long-term complications (nephrocalcinosis, kidney stones, brain calcifications, cataracts, etc.). HypoPT is a rare endocrine disease for which replacement therapy of deficient parathyroid hormone is not the standard treatment option (8). Patients are at risk of many complications such

Corresponding Author: Zafer Pekkolay, drpekkolay@gmail.com
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as kidney failure, psychiatric diseases, and infections. In addition, patients often have neurocognitive complaints. Symptoms such as inability to focus and concentration problems are observed (9).

This study aims to investigate real-life data of patients with hypoparathyroidism.

MATERIAL AND METHOD

Approval for the study was granted by the Non-Interventional Studies Ethics Committee of Dicle University Medical Faculty (Date: 14.11.2019, Decision No: 245). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective case-control study was conducted between 1 January 2010 and 31 December 2019 by examining the records of the hypoparathyroidism database of Dicle University Faculty of Medicine, Department of Endocrinology, which is a tertiary endocrine center.

The physician confirmed the diagnosis of permanent hypoparathyroidism was confirmed that calcium and active vitamin D treatment continued to keep serum calcium in the normal range in the sixth post-operative month, and PTH level was below average at least once.

In our study, the demographic data of the patients (age, gender), laboratory parameters at the time of admission (Ca, albumin, P, Mg, ALT, Cr, PTH, 25-OH Vit D, calcium in 24-hour urine, hemogram) were examined by the information in the hospital records. The device used for PTH measurement is Siemens Advia Centaur XP; the method used is an immunoassay, reference values are 15-65 pg/ml.

Patients with post-operative hypoPT, autoimmune hypoPT, and idiopathic hypoPT were included in the study. The patients were selected from patients aged >18 <80 years, and patients with diseases other than hypoPT complications (such as hypertension, vascular diseases) were not included in the study. The control group included people aged 15-79 years, with normal PTH levels and 25-OH Vit D >20 ug/L without any other disease.

The patients complications of hypoPT (nephrolithiasis, cataract, basal ganglia calcification) were analyzed from hospital records.

Statistical analyzes of the results obtained in the study were performed using SPSS (Statistical Package for the Social Sciences) 22 statistical software packages. Descriptive statistics for continuous variables from the parameters in the study will be expressed as mean ± standard deviation, minimum and maximum values, and categorical variables will be expressed as numbers and percentages. Student's t-test data of patient group and control group; Chi-square test will be used to analyze categorical variables. The statistical significance limit will be accepted as $p<0.05$.

RESULTS

Sixty-five patients (mean age 42.80±13.4 years, 91% female) with hypoPT, and 54 healthy controls (mean age 33.58±11.9 years, 65% female) were included. Mean calcium level 7.95±0.92 mg/dl, and mean PTH level 9.99±6.30 pg/ml in hypoPT patients. Regarding the etiology of hypoPT, 51(78%) patients had hypoPT due to surgery; 14 (22%) patients developed hypoPT due to non-surgical causes. In patients with hypoPT who underwent surgery, the mean calcium level was 8.03±0.93 mg/dl; The mean calcium level in patients with non-surgical hypoPT was 7.67±0.85 mg/dl. While the mean PTH level was 10.16±6.21 pg/ml in patients with hypoPT who underwent surgery, in non-surgical patients with hypoPT, the mean was 9.36±6.82 pg/ml. The most common surgery was due to multinodular goiter (72%). Twelve percent of the patients had thyroid cancer surgery. In 46 percent, the most common treatment was calcitriol 0.5 mcg/day and calcium 2000 mg/day. Nearly half of the patients had treatment non-compliance (46%). A cataract is present in two patients. Three patients had basal ganglia calcification. Twelve patients had kidney stones. Forty-three percent of the patients had been hospitalized in the last year. The most common reason for hospitalization was symptomatic hypocalcemia. The most common reason for this was treatment non-compliance. The most frequent follow-up frequency of the patients was three months (**Table 1**). The data of patients with hypoPT and the control group are compared in **Table 2**.

Table 1. Characteristics of patients with hypoparathyroidism

n	65
Female	90.7%
Age(year)	42.80±13.37
Ca (mg/dl)	7.95±0.92
PTH (pg/ml)	9.99±6.30
Surgical/non-surgical (n)	51/14
Most common surgery	Multinodulary goitre (72%)
Malignancy	12.3%
Graves disease	4.6%
Nephrolithiasis	18.4%
Reason for hospital readmission	Treatment non-compliance (46%)

Table 2. Comparison of hypoparathyroidism group and control group

	Hypoparathyroidism	Control	p value
n	65	54	NS
Gender (F/M)	56/9	35/16	<0.05
Age (year)	42.80±13.37	33.58±11.9	<0.05
Ca (mg/dl)	7.95±0.92	9.39±0.35	<0.05
PTH (pg/ml)	9.99±6.30	46.76±11.01	<0.05
25 OH D-vit (ug/L)	23.35±9.14	>20	NS
P (mg/dl)	4.45±0.94	3.56±0.36	<0.05
Mg (mg/dl)	1.72±0.17	1.83±0.15	NS

DISCUSSION

HypoPT; is a chronic disease characterized by hypocalcemia, hyperphosphatemia. The parathyroid hormone is low or normal. Surgery is the most common cause of acquired hypoPT, accounting for 75% of all cases. Non-surgical causes of hypoPT include autoimmune, genetic diseases, infiltrative, metastatic, radiation, mineral deposition, magnesium deficiency or excess, or idiopathic causes (1-3).

In our study, the most common cause of hypoPT was surgical, with 78%. The type of surgery with the highest risk of hypoPT is head and neck surgery. Performing thyroid surgery in centers of excellence reduces the risk of surgery related hypoPT (10). Another reason that increases the risk of hypoPT is secondary/completion surgeries. Completion surgery has been found to increase the risk of hypoPT in patients who have undergone hemithyroidectomy. Failure to localize the parathyroid glands by the surgeon in initial surgery and complementary surgery is a risk for permanent hypoPT (11). In our study, the most common cause of hypoPT (72%) was total thyroidectomy due to multinodular goiter. Anterior neck surgery is the most common cause of acquired hypoPT and is responsible for almost three-quarters of cases (1)

In the literature, the age of occurrence of hypoPT is generally in the fourth decade (1). In our study, the mean age of patients with hypoPT was 42 years. The reason why hypoPT is seen at these ages seems to be related to the increased frequency of surgeries about multinodular goiter at this age (12).

HypoPT is a disease primarily seen in women, and this may be related to the increased frequency of surgery for thyroid nodules in women. In our study, 90,7% of the patients were female, and 9,3% were male. In the literature, at least 75% of the patients are women, just as in our study. Apart from the multinodular goiter etiology of hypoPT, the frequent occurrence of autoimmune diseases in women may explain this rate (13).

In our study, 0.5-1 mcg/day calcitriol and 1-3 g calcium/day were used to achieve target calcium and phosphorus levels in most of our patients with hypoPT. Our literature review suggests that the oral calcium dose for adults with stable chronic hypoPT in the guidelines is 1 to 2 g of elemental calcium daily, in divided doses. The starting dose of calcitriol is 0.25 mcg twice daily with weekly dose increments to achieve low normal serum calcium. Most adults need up to 2 mcg per day. Vitamin D requirements vary significantly from patient to patient, and the correct dose in any given patient can be determined in the patient's biochemical follow-up (14).

In our study in patients with hypoPT, the most common complications were found to be renal and neurological complications. In the study of Underbjerg L. et al. (15) in Denmark, the risk of all types of renal disease was found to be significantly higher in both surgical hypoPT patients and non-surgical hypoPT patients compared to the general population. Patients with post-surgical hypoPT have a 4-fold increased risk of hospitalization for kidney stone disease.

Basal ganglia calcification in patients with hypoPT is related to the deterioration of calcium/phosphorus balance and is mostly associated with phosphorus elevation. According to the study of Shoback DM et al. (6), the primary biochemical abnormalities of hypoPT are hypocalcemia and hyperphosphatemia. While hypocalcemia causes most neuromuscular symptoms and signs of hypoPT, hyperphosphatemia contributes significantly to ectopic mineralization in soft tissues (vascular system, brain, kidneys, and other organs). The basal ganglia calcification rate of the patients in our study was 4.6%; the Intrarenal calcification rate was determined as 18%. In the study of Mitchell et al. 31% of the patients had intrarenal calcification, and 52% of them had basal ganglia calcification (16). The form of calcification may be more extensive involvement in the brain in some patients, mainly in the basal ganglia.

In our study, the most common hospitalization reason was due to hypocalcemia. In the study conducted by Underbjerg L et al. (17) in Denmark, hospitalizations due to seizures and symptomatic hypocalcemia increased ten times, and hospitalizations due to kidney stones and kidney damage increased six times.

Our study has some limitations; retrospective study design, the number of patients is small, complications related to hypoPT have not been investigated in detail in all patients and include only data from a tertiary endocrine center.

In conclusion, in our study, the most common cause of hypoparathyroidism is surgery due to multinodular goiter. The most common reason for hospitalization is treatment non-compliance. Up to one-fifth of patients had kidney stones.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Non-Interventional Studies Ethics Committee of Dicle University Medical Faculty (Date: 14.11.2019, Decision No: 245).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Effects of contrast medium exposure on urine albumin/creatinine ratio

Sanem Kayhan, Fatih Kıvrakoğlu, Ayşenur Miray Yarlıoğlu, Mercan Tastemur, Seyit İbrahim Akdağ

University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Internal Medicine, Ankara, Turkey

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ABSTRACT

Aim: Albuminuria is a direct consequence of renal glomerular injury and increases with glomerular dysfunction. Spot urine albumin/creatinine (Alb/Cr) ratio is a reasonable surrogate for 24-hour urine albumin excretion rate and certainly not without limitations. It is known that renal function can be affected following contrast agent administration. The aim of our study is to assess the changes in Alb/Cr ratio in spot urine before and after contrast agents in patients undergoing computed tomography (CT) scanning.

Material and Method: The present study included 103 hospitalized patients aged between 18 and 75 years, who underwent contrast-enhanced CT scanning for any reason and did not develop contrast-induced nephropathy (CIN). We compared the values of Alb/Cr ratio at the 6th, 12th, 24th, 48th, and 72nd hours after the procedure (post-procedure time) with the values at pre-procedure time.

Results: The median age of the patients were 61 years. It has been observed that there is no significant increased in microalbuminuria after the use of contrast media. When the patients were evaluated for the albuminuria level before the procedure, it has been seen that 73 patients (70.9%) had an Alb/Cr ratio of <30 mg/g (group-1) and 30 patients (29.1%) had an Alb/Cr ratio of ≥30 mg/g (group-2). In group 1, it has been observed that the Alb/Cr ratios at the post-procedure 6th, 12th, 24th, and 48th hours were statistically significantly higher than the value at pre-procedure time. In group 2, it has been observed that Alb/Cr ratio values at all post-procedure time except the 24th hour were statistically significantly lower than the values at the pre-procedure time.

Conclusion: It should be considered that there might be changes in Alb/Cr ratio even without developing significant complications such as CIN in patients exposed to contrast medium.

Keywords: Contrast medium, urine albumin/creatinine ratio, microalbuminuria

INTRODUCTION

Contrast-induced nephropathy (CIN) is an important complication that develops as a result of exposure to contrast media during diagnostic procedures such as computed tomography (CT) and angiography. It is characterized by iatrogenic acute kidney injury within 24-72 hours after intravascular injection of iodine-based radiocontrast agents (1-3). CIN constitutes 10% of hospital-acquired acute kidney injuries (2). Moreover, it is associated with prolonged hospital stay, increased cardiovascular and renal morbidity, and all-cause mortality (4,5). On the other hand, it is proposed that renal function can be affected following contrast agent administration even if CIN does not occur. For this reason, it is suggested that attention must be paid to renal function in patients not developing CIN, and that renal functions of patients exposed to contrast agents need to be followed up for a long period (4,6).

Biochemical changes in the serum and urine of people exposed to intravenous contrast medium are generally transient. Proteinuria is one of these changes (4). Proteinuria and pH changes determined using urine dipstick testing within 24 hours after the administration of the contrast agents mostly occur due to the presence of contrast medium in the urine and should be interpreted with caution (7,8). Although there are studies on the potential analytical interference of contrast media in laboratory diagnostics, it is important to emphasize that sample quality and integrity may also be affected by the problems caused by these compounds (9).

Corresponding Author: Sanem Kayhan, drkayhansanem@yahoo.com

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Proteinuria can be detected by semiquantitative (dipstick urinalysis) or quantitative (24-hour urine protein test or albumin/creatinine [Alb/Cr] ratio in a spot urine samples) tests (10). Dipstick urinalysis is a widely used, conventional, quick and easy method. Urine protein concentrations >10-20 mg/dL can be detected with this test (11). However, the dipstick test may give false positive and negative results. Alkaline or concentrated urine may result in false positive results, while acidic or diluted urine may result in false negative results (12). In that case, quantitative tests, 24-hour urine protein test, or Alb/Cr ratio in spot urine, should be performed to verify the results. Spot urine test is preferred, as it is more easily performed in comparison to 24-hour urine test (11). While the spot urine albumin/creatinine (Alb/Cr) ratio is a valid substitute for 24-hour urine albumin excretion rate, it has its limitations (13).

It has been acknowledged that measurement of serum creatinine as an indicator of kidney dysfunction is not an ideal method and even Modification of Diet in Renal Disease (MDRD) and Cockcroft Gault methods have their limitations. Albuminuria, a known marker for the progression of chronic renal disease, is a direct consequence of glomerular damage and increases in glomerular dysfunction (13). It has been previously shown that contrast agent has toxic renal effects such as enzymuria and proteinuria without causing nephropathy (7,14). In this study, we aimed to quantitatively (using the urinary Alb/Cr ratio) demonstrate the potential effect of a contrast agents, without causing significant renal dysfunction, on glomerular albumin loss, in patients who underwent CT for various reasons.

MATERIAL AND METHOD

The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Date: 27.03.2017, Decision No: 36/28). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consents of all patients were obtained before inclusion. This study was designed as a single-center, prospective observational study.

Among the patients hospitalized in our clinic, those aged between 18 and 75 years, who underwent contrast-enhanced CT scanning for any reason (staging of acute pancreatitis, malignancy, investigation of the etiology of anemia, etc.) and patients who did not have any complications (CIN, allergy, etc.) after contrast agent were included in the present study. The patients with NYHA (New York Heart Association) class III-IV heart failure and who had renal dysfunction (abnormal serum creatinine levels and a glomerular filtration rate (GFR) < 60 mL/min/1.72m^2) were not included in the present study. Advanced age (>75), heart failure and known kidney disease are important risk factors for CIN (5). Therefore, at the beginning of the study, these groups of patients with a high probability to develop CIN, were not included in the study. In the follow-up, patients diagnosed with CIN according to the European Society of Urogenital Radiology (ESUR) guideline were excluded from the study. CIN was defined as the 25% or 0.5 mg/dl increase in serum creatinine levels from baseline within 2-3 days after contrast agent administration without the presence of any other etiological causes (3).

The same contrast agent (iohexol) in the same amount (90 mL) was used in all patients. Due to the presence of at least one risk factor for contrast nephropathy (diabetes mellitus, use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or diuretics, advanced age) in all patients of our study, 0.9% sodium chloride was administered to all patients 6-12 hours before the procedure and in a 12-24 hour period after the procedure via intravenous route at a dose of 1 mg/kg/hour. In addition, 2x1200 mg N-acetylcysteine was given via oral route. The Alb/Cr ratio in spot urine was measured both before the CT procedure (pre-procedure time) and at the 6th, 12th, 24th, 48th, and 72nd hours after the CT procedure (post-procedure time). Previous studies have shown that, in CIN pathophysiology, renal damage begins earlier (<4 hours), before the disruption in creatinine levels (15). Therefore, in our study, we preferred to take measurements also at the 6th, 12th, and 24th hour time points. We aimed to compare the values within the different periods according to the time of performing CT procedure (between pre-procedure time value and post-prosedure time values). The hypothesis of this study is not to compare repeated measures in multibl. Urine albumin and creatinine concentrations were evaluated immediately in the central laboratory with a Beckman Coulter AU5800 (CA, USA) instrument, using the turbidimetric method for urine albumin and the kinetic Jaffe procedure for urine creatinine. According to KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline urine albumin-to-creatinine ratio was calculated and the results were divided into 2 categories: (1) normoalbuminuria; Alb/Cr ratio <30 mg/g (group-1); (2) microalbuminuria; Alb/Cr ratio ≥30 mg/g (group-2) (16).

Statistical Analysis

Data were analyzed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Normality distribution analysis of the data was performed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed numerical data were expressed as mean±SD, non-normally distributed numerical data were expressed as median (interquartile range, IQR

25-75%). Wilcoxon Signed Rank Test was used for dependent group pairwise comparison analysis between pre-procedure measurements and post procedure 6th, 12th, 24th, 48th, and 72nd hour measurements. P value <0.05 was considered statistically significant.

RESULTS

The median age of the 103 participants (55.3% female) included in the present study was 61(47-71) years. General characteristics of the patients are seen in **Table 1**. Comparison of Alb/Cr ratio at each time point with pre-procedure values is seen in **Table 2**. Alb/Cr ratio at the post-procedure 72nd hour was significantly lower than the pre-procedure value. There was no significant change in GFR values at any time point. The decrease in urea and creatinine values at only post-procedure 48th hour was statistically significant compared to the pre-procedure values.

When the patients were evaluated for the albuminuria level before the procedure, it has been seen that 73 patients (70.9%) had an Alb/Cr ratio of <30 mg/g (group-1) and 30 patients (29.1%) had an Alb/Cr ratio of ≥30 mg/g (group-2). In group-1; it has been observed that the Alb/Cr ratio at the post-procedure 6th, 12th, 24th, and 48th hours was significantly higher than the value at pre-procedure time, while the Alb/Cr ratio at the post-procedure 72nd hour was similar to the value at pre-procedure time. In group 2, it has been observed that Alb/Cr ratio values at all post-procedure time except the 24th hour were statistically significantly lower than the values at the pre-procedure time (**Table 3**).

The percentage of diabetic patients was similar in the groups with and without pre-procedure microalbuminuria (p=0.24); 27 (37.5%) patients in the group with an Alb/Cr ratio <30 and 15 (50%) patients in the group with an Alb/Cr ratio ≥30 had diabetes.

Table 1. General characteristics of the patients

	n=103
Gender	
Female, n (%)	57 (55.3)
Male, n (%)	46 (44.7)
Age, years	61 (47-71)
The reason for having CT scan	
Malignancy, n (%)	47 (45.6)
Pancreatitis, n (%)	27 (26.2)
Anemia, n (%)	15 (14.6)
Mass, n (%)	4 (3.9)
Other, n (%)	10 (9.7)
Diabetes, n (%)	42 (40.7)
Hb1Ac, %, median (IQR 25-75%)	7.2 (5.9-11.8)
Hypertension, n (%)	37 (35.9)
Urinary protein dipstick test before the procedure	
Negative	101 (98.1)
1+	1 (1.0)
2+	1 (1.0)
Pre-procedure	
Serum urea, mg/dL, median (IQR 25-75%)	29 (22-39)
Serum creatinine, mg/dL, median (IQR 25-75%)	0.8 (0.7-0.9)
GFR, mL/min/1.73m^2, median (IQR 25-75%)	84 (70.1-102)
Urine Alb/Cr ratio, mg/g, median (IQR 25-75%)	16.5 (7.7-38.2)

CT, computed tomography; GFR, glomerular filtration rate; Alb/Cr, albumin/creatinine; IQR, interquartile range Data are presented as number (%) or median (Q1-Q3), where appropriate.

Table 2. The comparison of changes in the albumin/creatinine ratio between each specific time point of the post-procedure time and the pre-procedure time

Alb/Cr ratio (n=103)	median (IQR 25-75%)	p*
Pre-procedure	16.5 (7.7-38.2)	0.37
Post-procedure 6th hour	15.7 (8-38.2)	
Pre-procedure	16.5 (7.7-38.2)	0.15
Post-procedure 12th hour	15.6 (9.3-28.8)	
Pre-procedure	16.5 (7.7-38.2)	0.79
Post-procedure 24th hour	15.9 (9-33)	
Pre-procedure	16.5 (7.7-38.2)	0.23
Post-procedure 48th hour	16.5 (9.1-33.3)	
Pre-procedure	16.5 (7.7-38.2)	0.046
Post-procedure 72nd hour	15.1 (8-27.2)	

GFR, glomerular filtration rate; Alb/Cr, albumin/creatinine; IQR, interquartile range
*Wilcoxon signed rank test.

Table 3. The comparison of changes in the albumin/creatinine ratio of patients without microalbuminuria (group-1) and with microalbuminuria (group-2) at the specific time point of the post-procedure time and the pre-procedure time.

	median (IQR 25-75%)	p*
Group-1 (Alb/Cr ratio <30) n=73		
Pre-procedure	9.8 (6.9-18)	0.046
Post-procedure 6th hour	13 (6.9-21.7)	
Pre-procedure	9.8 (6.9-18)	0.021
Post-procedure 12th hour	12.8 (8.6-20.9)	
Pre-procedure	9.8 (6.9-18)	0.020
Post-procedure 24th hour	12.6 (7.4-24.9)	
Pre-procedure	9.8 (6.9-18)	0.040
Post-procedure 48th hour	12.7 (6.8-21.7)	
Pre-procedure	9.8 (6.9-18)	0.79
Post-procedure 72nd hour	10.7 (7.3-18)	
Group-2 (Alb/Cr ratio ≥30) n=30		
Pre-procedure	58 (41.7-166.1)	0.002
Post-procedure 6th hour	41.4 (23.1-108.6)	
Pre-procedure	58 (41.7-166.1)	<0.001
Post-procedure 12th hour	30.2 (19.6-99.8)	
Pre-procedure	58 (41.7-166.1)	0.12
Post-procedure 24th hour	42.9 (22.7-112.2)	
Pre-procedure	58 (41.7-166.1)	0.002
Post-procedure 48th hour	39.9 (29.8-108.1)	
Pre-procedure	58 (41.7-166.1)	0.009
Post-procedure 72nd hour	43 (19-115)	

GFR, glomerular filtration rate; Alb/Cr, albumin/creatinine; IQR, interquartile range
*Wilcoxon signed rank test

DISCUSSION

The main finding of our study is that it has been seen that there is a significant increase in the urinary Alb/Cr ratio in patients with Alb/Cr ratio <30 mg/g after the use of nonionic low osmolar contrast material (Iohexol) used for CT, but this increase does not reach the level of microalbuminuria. It should be kept in mind that there may be changes in Alb/Cr ratio values in patients receiving contrast agent for CT procedures, even if complications such as CIN have not developed in these patients.

Besides the benefits of contrast agents commonly used in daily radiology practice, they also have undesirable effects. Intravenous contrast media use is sometimes necessary for diagnosis but mostly associated with transient biochemical irregularities. In a study by Okoye et al. (7), a significant decrease in serum sodium and potassium levels, a significant increase in serum urea, Cr, and urine pH were detected after exposure to the contrast agent, and these changes were reported to return to normal 72 hours after contrast agent exposure. In our study, it has been seen that the decrease in urea and creatinine values at only post-procedure 48th hour was statistically significant compared to the values at pre-procedure time. This was attributed to the hydration of all patients starting from before the procedure and lasting until the 48th hour after the procedure.

In addition, even without causing renal dysfunction, the contrast agent has many renal impacts such as proteinuria, enzymuria, and increased urinary pH (14,17). In their study investigating the effect of exposure to nonionic radiocontrast agents on microalbuminuria in patients undergoing angiography, Chu et al. (18) reported that ordinary dose low osmolar contrast agents had no significant effect on the presence and level of microalbuminuria. Again, as a result of a series of studies conducted by Holtas et al. (19,20), it was suggested that the actual cause of proteinuria observed after renal angiography may be due to the chemical structure of the contrast agent used and individual factors. The same researchers proposed that osmolality is not a dominant factor; and that proteinuria may occur due to the destruction in the kidney and vascular endothelium caused by the contrast media (19,20).

Similar to the study of Chu et al. (18), we found that there was no significant increase in Alb/Cr ratio after the procedure. The reason for these findings may be the use of low-dose contrast media in all patients and ensuring adequate hydration starting from before the procedure. However, when we divided the patients into groups according to the presence of microalbuminuria, we obtained different results. In the 73 patients constituting group-1; it has been observed that there were significant increases in Alb/Cr ratio in all of the repeated measurements up to the post-procedure 48th hour compared to the values at the pre-procedure time, but these increases did not reach the microalbuminuria level. Since we preferred to use the Alb/Cr ratio, which gives quantitative results, rather than the dipstick test, which is known to give false positive results in post-procedure albuminuria evaluations; we think that the contrast agent disrupts the permeability by causing temporary damage to the glomerular endothelium and causes a slight, transient increase in albuminuria.

In the 30 patients constituting group-2, it has been observed that Alb/Cr ratio at pre-procedure time was significantly lower than all post-procedure time measurements except the 24th hour measurement. This may be attributed to the fact that patients with microalbuminuria are not able to reflect the transiently increasing albuminuria due to the impaired glomerular membrane structure. Microalbuminuria occurs as a result of impaired glomerular permselectivity to plasma proteins, and whether there is a decrease in glomerular filtration rate, the presence of long-term microalbuminuria in the patient is defined as chronic kidney disease according to the guidelines prepared by the National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) (21). As in patients with microalbuminuria, the elimination time of the contrast agent is prolonged in individuals with impaired renal function (22). We believe that the osmotic diuretic effect will be more pronounced in these patients, and the Alb/Cr ratio may appear low. In addition, it should not be overlooked that compared to the normoalbuminuric group, our group was not large enough to evaluate the effect of contrast agents in microalbuminuric patients.

Our study has some limitations. Firstly, low-dose contrast agent was used in all patients. Secondly, we did not measure other specific urinary proteins (e.g.; transferrin or β2-microglobulin) or tubular enzymes. Finally, since we excluded patients with high risk for developing CIN, the results of our study are not valid for these patients.

CONCLUSION

In the present study, it has been shown that contrast material exposure during CT procedures may have negligible toxic effects on glomerular albumin loss and the changes in Alb/Cr ratio are transient. The results of the present study support our hypothesis that not only tubular damage but also glomerular damage may occur due to the use of contrast agents. Our study should be considered as a pilot study and further studies are needed to reveal the clinical significance of the transient increase in Alb/Cr ratio due to the contrast agent.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Date: 27.03.2017, Decision No: 36/28).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The relationship between the nutritional status, body-mass index of patients with chronic obstructive pulmonary disease and respiratory failure and their 1-year survival

Murat Yıldız[1], Deniz Çelik[2]

[1]Health Sciences University, Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Pulmonary Intensive Care Unit, Ankara, Turkey
[2]Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Pulmonology, Antalya, Turkey

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ABSTRACT

Aim: We aimed to determine whether chronic obstructive pulmonary disease (COPD) and respiratory failure patients' characteristics can be defined as additional criteria to Body Mass Index (BMI), Nutritional Risk Screening (NRS-2002), and Albumin affecting the 1-year mortality.

Material and Method: One hundred eighty-sixes patients who have been hospitalized in the Pulmonary Intensive Care Unit between 01.01.2019 and 31.12.2019 were included in our study.

Results: The study comprised 186 patients and 63.5% of them were male (n=118) and 36.5% were female (n=68). The 1-year mortality of the patients after discharge was evaluated in two groups: those who died within 1 year (n=87, 46.7%) and the survivors' group (n=99, 53.3%). We found a significant difference between the survivors and the deceased patients in terms of weight, nutrition score, number of stays in the hospital, number of readmissions to the emergency service after discharge, and NRS-2002 score ($p<0.05$). Cox regression analysis revealed that the number of stays in the hospital, NRS-2002 score, and C-Reactive Protein (CRP) variables significantly affect the survival of the patients ($p <0.05$). All patients were divided into two groups (NRS-2002<4 vs. NRS-2002≥4) according to the median value of NRS-2002. Thus, the survival analysis of two different groups was compared as a risk group and a high-risk group in terms of nutritional status. There was a statistically significant difference between the NRS-2002 groups in terms of survival times. The survival time of the cases in the NRS-2002 score ≥4 group was significantly lower than the cases in the NRS-2002 score <4 group.

Conclusion: We demonstrated that NRS-2002, CRP, and prolonged stay in the hospital have a relationship with the increased mortality risk. Combining NRS-2002 score ≥4 with elevated CRP levels at admission, may produce more accurate results in evaluating a patient's nutritional status in clinical practice and help make predictions about the patient's prognosis. More studies may evaluate the nutritional status of COPD patients, not only in hospitals but also in outpatient clinics.

Keywords: NRS-2002, COPD, respiratory failure, mortality

INTRODUCTION

Screening of nutritional risk has long been recommended by national and international associations. Nutritional risk has been defined to a great extent in patients with chronic obstructive pulmonary disease (COPD), and its prevalence (20-45%) varies depending on which screening tool is used (1). It has been suggested that if malnutrition is detected by the Nutritional Risk Screening (NRS-2002) screening tool in patients hospitalized with the diagnosis of acute bronchitis, COPD exacerbation, community-acquired pneumonia, these are associated with the worsening of the disease and is directly related to mortality Providing nutritional support to these patients has a positive effect on mortality (2). However, skeletal muscle weakness and loss of fat-free body mass (FFM) are coexist with COPD (3).

Nutritional risk screening (NRS-2002) tool was developed by the Danish Association for Parenteral and Enteral Nutrition. It has also been recommended for use by the European Society for Clinical Nutrition and Metabolism (ESPEN). A patient with a total score of 3 is considered to be "at nutritional risk" (1). In the PubMed search (NRS 2002 and COPD; search date 19.10.2021), there were 9 studies. Two of them were not relevant. In these 7 studies,

Corresponding Author: Deniz Çelik, drdenizcelik@hotmail.com
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only one of them was included patients with COPD and Respiratory failure. In their study, Chen et al. (7) included COPD patients with respiratory failure. They found that Body Mass Index (BMI) and serum albumin values independently predicted in-hospital mortality. BMI and NRS-2002 predicted 1-year mortality, and it was determined that all three methods (BMI, NRS-2002, and Albumin) predicted rehospitalization within the 30 days after the discharge. Our study will be the second study with the same diagnosis and we aimed to find an additional criterion in predicting the 1-year mortality.

Our hospital is a tertiary chest diseases hospital and our pulmonary intensive care unit is specialized in COPD patients who developed acute or acute-on-chronic respiratory failure. Respiratory failure occurs in the end stage of COPD. Frequent exacerbations are common and patients are in a 'never-ending inflammation' process. Inflammation triggers the catabolic process. We observed that our patients were mostly malnourished and the prognosis of these patients was worst. The nutritional habits are mostly cultural and the way of expressing is subjective. This study comprised patients with only COPD and respiratory failure in a specific ICU.

We hypothesized that a single, simple and easy screening tool could be effective to predict malnutrition earlier in this patient population.

We aimed to determine the COPD and respiratory failure patient's characteristics as an additional criterion to BMI, NRS-2002 score, and albumin levels in predicting the 1-year mortality.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Keçiören Education and Training Hospital Clinical Studies Ethics Board (Date: 14.09.2021 Decision No: 2012-KAEK-15/2355). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Selection of Patients

One-hundred eighty-six patients who have hospitalized in the Pulmonary Intensive Care Unit between 01.01.2019 and 31.12.2019 were included in our study. All patients whose data were available and who gave consent for clinical studies at admission were included in the study. The study design is cross-sectional.

Inclusion Criteria

All COPD and respiratory patients hospitalized in the pulmonary intensive care unit (ICU) have been included in the study. For obtaining real-life data, the patients who had comorbidities didn't exclude. The patients with COPD were diagnosed and treated by a pulmonologist before and had received inhalation therapies for a long period. All patients admitted to the Emergency room of our hospital. Our hospital is a tertiary chest diseases hospital and the Emergency room team consists of pulmonologists and pulmonology residents. All patients' primary diagnosis was COPD exacerbations and/or decompensation of respiratory failure. The indications of pulmonary ICU hospitalizations were either severe exacerbation and/or decompensation of respiratory failure. All patients' Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications consisted of group D.

Exclusion Criteria

We planned to perform post-discharge survival analysis, so we excluded only malignancy patients. The patients who died in the hospital (who could not be discharged) were excluded too.

Nutritional Risk Screening-2002 (NRS-2002)

NRS-2002 is a screening system developed by Kondrup et al. (8) based on the retrospective analysis of randomized controlled trials. NRS-2002 was recommended by the ESPEN and was developed for malnutrition risk screening in hospitalized patients within the first 48 hours following hospitalization. The Turkish validation study of the scale was done by Bolayır in 2014 (9). Nutrition screening and evaluation were done using the three-component of the NRS-2002 screening tool. The first component evaluates the nutritional status with three separate items. The nutritional status' is scored between 0-3 points. The first component consists of the following: BMI category (<20.5 or >20.5), weight loss category [>5% at 3 months, >5% at 2 months and >5% at 1 month (>15% at 3 months)], and decreased food intake as a proportion of normal need in the previous week (0% 25, 25-50%, 50-75% and >75%). If the answer to any of these three questions is yes, the second stage of the scoring system is started.

The second and third components assess disease severity and age, respectively. The disease severity is scored between 0-3 points. 1 point includes patients with chronic illnesses who have been hospitalized for complications. These patients are debilitated but may get out of the bed regularly. Protein requirement is increased, but is mainly at a level that can be overcome with oral diet and supplementation. 2 point represents patients who have become bedridden due to infection or major abdominal surgery as a prototype. Protein requirements are markedly increased and in most cases, artificial feeding may be required. 3 points consist of patients in need of intensive care, under inotropic or ventilatory support as a prototype. Finally, all patients over the age of 70 receive an additional score increase. If the total score is 3 or more; the patient is at nutritional risk and a nutritional plan is initiated. If the score is <3; should be scanned once

a week. If there is a major surgical operation planned, a nutrition plan should also be developed. The BMI cut-off value for malnutrition diagnosis is 18.5 kg/m² (8).

Statistical Method

Analyzes were made with the Statistical Package for the Social Sciences (SPSS) Statistics 26 package program. When analyzing the data, the frequencies (number, percentage) were given for categorical variables; while descriptive statistics (mean, standard deviation) were given for numerical variables. Normality assumptions of numerical variables were examined with the Kolmogorov Smirnov normality test and it was observed that the variables were normally distributed. For this reason, parametric statistical methods were used in the study. The differences between the two independent groups were analyzed using the Unpaired T-Test. Relations between two categorical variables were checked with Chi-Square analysis. Fisher's Exact Test was used when the expected value assumption was not provided in the Chi-Square analysis. The survival duration of the patients was examined with Kaplan Meier analysis, and variables affecting survival were checked with Cox Regression analysis. Statistical significance in the analyzes was interpreted at the level of 0.05 for the p-value.

The study was designed as cross-sectional and analyzed patients hospitalized whole 1 year. In the retrospective power analysis for the adequacy of the survival analysis, at a significance level of 0.05 and an effect width of 0.8; the power of the study was calculated as 97.3%.

RESULTS

The study comprised 186 patients and 63.5% of them were male (n=118) and 36.5% were female (n=68). The 1-year mortality of the patients after discharge was evaluated in two groups: those who died within 1 year after discharge (n=87, 46.7%) and the survivors' group (n=99, 53.3%) (**Table 1**).

The relation between the comorbidities and mortality was analyzed. A statistically significant relationship was found between the presence of Acute or Chronic Renal Disease and mortality (p=0.016).

Table 1. Conditions and comorbidities that affect mortality

		Survivor group (n=99)		Exitus group (n=87)		p
		n	%	n	%	
Gender	Female	31	45.6	37	54.4	0.113
	Male	68	57.6	50	42.4	
Age (year)		67.00±12.43		74.30±11.82		0.000*
Readmission to the hospital after discharge		30	53.6	26	46.4	0.951
Readmission to the emergency room within 30 days after discharge		13	52.0	12	48.0	0.895
Readmission to the hospital within 30 days after discharge		9	52.9	8	47.1	0.980
Domiciliary long term oxygen therapy		90	55.9	71	44.1	0.064
Domiciliary noninvasive mechanical ventilation		39	54.9	32	45.1	0.714
Bronchiectasis		10	76.9	3	23.1	0.076
Pulmonary hypertension		6	66.7	3	33.3	0.506
Sleep apnea or obesity hypoventilation syndrome		6	66.7	3	33.3	0.506
Central nerveus system diseases		7	41.2	10	58.8	0.296
Decompensated respiratory acidosis		6	50.0	6	50.0	0.817
Acute bronchitis		5	55.6	4	44.4	1.000
Bening prostate hyperplasia		7	63.6	4	36.4	0.476
Pulmonary sequelae due to tuberculosis		7	70.0	3	30.0	0.341
Other metabolic diseases		6	75.0	2	25.0	0.287
Pleurisy		1	20.0	4	80.0	0.187
Rheumatic diseases		1	33.3	2	66.7	0.600
Pneumonia		20	42.6	27	57.4	0.090
Pulmonary thromboembolism		10	41.7	14	58.3	0.224
Restrictive lung disease		12	70.6	5	29.4	0.132
Diabetes mellitus		22	55.0	18	45.0	0.800
Congestive heart failure		20	44.4	25	55.6	0.175
Coronary artery disease		16	48.5	17	51.5	0.547
Acute or chronic renal disease		2	18.2	9	81.8	0.016*
Atrial fibrillation		6	35.3	11	64.7	0.120
Hypertension		43	58.9	30	41.1	0.212
Hypoxic respiratory failure		15	55.6	12	44.4	0.793
Hypercapnic respiratory failure		57	58.8	40	41.2	0.114

*:p<0.05

There were no significant differences between the survivors and the exitus group in terms of gender, rehospitalization after discharge, presence of NRS-2002 itself and, its scoring.

We found a statistically significant difference between the survivors and the deceased patients in terms of weight, nutrition score, number of stays in the hospital, number of readmissions to the emergency service after discharge, and NRS-2002 score (p<0.05) (**Table 2**).

Table 2. Distribution of patient characteristics

	Survivor group (n=99)		Exitus group (n=87)		p
	Mean	SD	Mean	SD	
Height	165.06	9.74	163.29	7.85	0.178
Weight	75.41	17.87	69.79	18.60	0.038*
Body mass index	27.83	7.05	26.23	6.96	0.124
Disease severity score	2.61	0.79	2.67	0.74	0.593
Nutrition score	0.40	0.55	0.57	0.62	0.049*
NRS 2002 score	3.36	1.16	3.93	1.07	0.001*
Number of stay in hospital (day)	11.69	6.64	17.48	13.26	0.000*
Number of hospitalizations after discharge (n=56)	1.70	0.46	1.70	0.46	0.951
Number of admissions to the emergency room after discharge (n=90)	1.44	0.50	1.60	0.49	0.037*
COPD diagnosis duration (year)	6.06	6.32	5.83	6.19	0.800

t: Unpaired T-Test, *:p<0.05, COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

The weight of the exitus group was significantly less than the survivors. In addition, the nutritional score, the number of stays in the hospital, the number of readmissions to the emergency service after discharge, and the NRS-2002 score levels of the exitus group are significantly higher than the survivors.

The relationship between the laboratory values and mortality was presented in **Table 3**.

Table 3. Descriptive statistics of laboratory measurements by mortality status

	Survivor group (n=99)		Exitus group (n=87)		p
	Mean	SD	Mean	SD	
Blood urea nitrogen	20.65	10.78	26.30	15.37	0.004*
Uric acid	5.58	2.04	6.14	2.44	0.093
Albumin	34.74	4.66	33.69	4.97	0.137
Hemoglobin	14.38	2.53	13.26	2.47	0.003*
Creatinine	0.95	0.39	1.12	0.86	0.085
C-reactive protein	57.72	69.87	85.98	104.75	0.034*
Total protein	62.79	6.18	62.29	7.40	0.615
Hematocrit	46.86	8.16	43.22	8.20	0.003*
White blood cell	11047.84	4691.13	11970.46	6759.97	0.276
APACHE-II score	12.27	4.42	13.65	4.49	0.037*

t: Unpaired T-Test, *: p<0.05, APACHE-II: Acute Physiologic Assessment and Chronic Health Evaluation II, SD: Standard deviation

There is a statistically significant difference between the survivors and the exitus group in terms of Blood Urea Nitrogen (BUN), Hemoglobin, C-Reactive Protein (CRP), Hematocrit, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores (p<0.05). While the hemoglobin and hematocrit levels of the survivors were significantly higher; the BUN, CRP, APACHE II scores of the exitus group were significantly higher than those of the survivors (**Table 3**).

Determination of the Variables Affecting Survival

Variables affecting the mortality of patients were included in the Cox Regression model as an independent variable. The variables included in the model were readmission to the emergency room after discharge, weight, nutritional score, number of stays in the hospital, NRS-2002 score, acute or chronic renal disease status, BUN, Hemoglobin, CRP, Hematocrit, and APACHE II score. Among these variables, the assumption of risk invariance for the categories of readmission to the emergency room after discharge and acute or chronic renal disease status, which are categorical variables, was analyzed graphically and the variables were considered appropriate to be included in the model. The absence of a high correlation between independent variables, which is another important assumption of Cox regression, was analyzed from the correlation table of the Cox Regression Analysis; and high correlations were observed between NRS-2002 score and nutritional score and between Hemoglobin and Hematocrit. Therefore, nutritional score and Hematocrit variables were excluded from the model. Later, the model was run by utilizing the Backward Wald method. When the results were examined, it was understood that the most suitable model was established in 6 steps and weight, hemoglobin level, APACHE II score, and acute or renal disease variables were excluded from the model. The results for the remaining variables are shown in **Table 4**.

When **Table 4** is examined, it can be seen that after the exclusion of the variables, the number of stays in the hospital, NRS-2002 score, BUN, and CRP variables remained in the model. When the Omnibus test results are examined, the established Cox Regression model is statistically significant (p<0.05). When the coefficients of the independent variables in the model are examined, it can be inferred that the number of stays in the hospital, NRS-2002 score, and CRP variables significantly affect the survival of the patients statistically (p<0.05). As a result, when the number of stays in the hospital increases by 1 unit, the risk of death increases by 1.036 times. When the NRS-2002 score increases by 1 unit, the risk of death increases by 1.337 times. When CRP increases by 1 unit, the risk of death increases by 1.002 times.

Table 4. Analysis of variables that affect survival						
	B	Standard Error	p	Exp(B)	%95 Confidence Interval Exp (B)	
					Lower Bound	Upper Bound
Number of stay in the hospital (days)	0.036	0.009	0.000*	1.036	1.019	1.054
NRS-2002 score	0.290	0.105	0.006*	1.337	1.088	1.643
Blood urea nitrogen	0.015	0.008	0.054	1.015	1.000	1.030
C-reactive protein	0.002	0.001	0.034*	1.002	1.000	1.005
Omnibus Test Chi Square=47.186 p=0.000						

NRS-2002 scores were naturally high in both groups due to the high risk of malnutrition in the patient groups (3.36±1.16 vs 3.93±1.07). In our study, the vast majority of patients were elderly, and the fact that the patients were hospitalized in the intensive care unit. All patients were divided into two groups (NRS-2002<4 vs NRS-2002≥4) according to the median value of NRS-2002. Thus, the survival analysis of two different groups was compared as a risk group and a high-risk group in terms of nutritional status (**Table 5**).

Table 5. Survival analysis by NRS-2002 groups (Kaplan Meier)				
NRS-2002 score	Survival Period (days)	Survival Rate		Total Case Number
		Estimate	Standard Error	
NRS-2002<4 (n=71)	90	0.873	0.039	9
	180	0.859	0.041	10
	365	0.746	0.052	18
NRS-2002≥4 (n=115)	90	0.739	0.041	30
	180	0.643	0.045	41
	365	0.557	0.046	51

As a result of Kaplan Meier analysis, the patients who have the NRS-2002 score <4, the 90-day survival rate is 87.3%, the 180-day survival rate is 85.9%, and the 1-year survival rate is 74.6%. the patients who have the NRS-2002 score ≥4, the 90-day survival rate is 73.9%, the 180-day survival rate is 64.3%, and the 1-year survival rate is 55.7%.

The survival time of the patients in the NRS-2002 <4 group was 602,769 days, while the patients in the NRS-2002 ≥4 group were 422,767 days (**Table 6**). There was a significant difference between the NRS-2002 groups in terms of survival times. The survival time of the patients in the NRS-2002<4 group was significantly higher than the patients in the NRS-2002 ≥4 group (p<0.001). **Figure 1** shows survival analysis according to NRS-2002 groups

In a summary, in this specific group of patients with COPD and respiratory failure, the patients have been divided into two groups as survivors and exitus groups in 1-year follow-up after discharge. Gender, weight, rehospitalization after discharge, presence of domiciliary LTOT, or domiciliary NIV were not significant between the two groups. Nutrition score, BUN, Hemoglobin, CRP, Hematocrit, APACHE II scores, number of

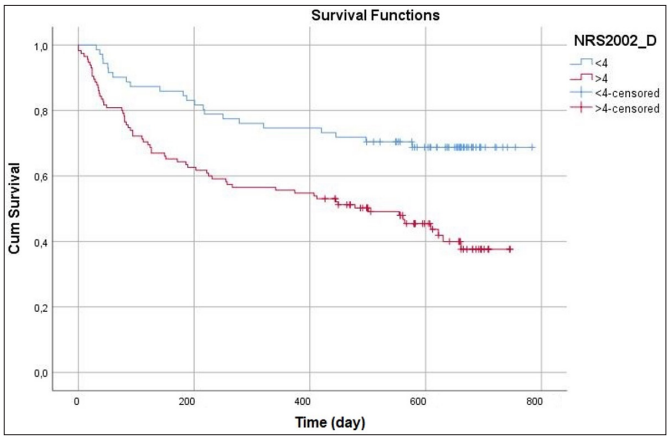

Figure 1. Survival analysis according to NRS-2002 groups.

stays in the hospital, number of readmissions to the emergency service after discharge, and NRS-2002 score were significant between the two groups. There was a significant relationship between the presence of Acute or Chronic Renal Disease and mortality.

Variables affecting the mortality of patients were included in the Cox Regression model, each one as an independent variable. The variables included in the model were readmission to the emergency room after the discharge, weight, nutritional score, number of stays in the hospital, NRS-2002 score, acute or renal disease status, BUN, Hemoglobin, CRP, Hematocrit, and APACHE II score. The most suitable model was established in 6 steps and weight, hemoglobin, APACHE II score, and acute or renal disease variables were excluded from the model. The number of stays in the hospital, NRS-2002 score, BUN, and CRP variables remained in the model. The number of stays in the hospital, NRS-2002 score, and CRP variables significantly affect the survival of the patients (p<0.05). All patients were divided into two groups (NRS-2002<4 vs NRS-2002≥4) according to the median value of NRS-2002. Thus, the survival analysis of two different groups was compared as a risk group and a high-risk group in terms of nutritional status. There was a significant difference between the NRS-2002 groups in terms of survival times. The survival time of the patients in the NRS-2002 score ≥4 group was significantly lower than the patients in the NRS-2002 score <4 group.

Table 6. Survival period by NRS-2002 groups

NRS-2002 score	Mean		95% Confidental Interval		Median		95% Confidental Interval	
	Survival	Standard Error	Lower Limit	Upper Limit	Survival	Standard Error	Lower Limit	Upper Limit
<4	602.769	33.703	536.71	668.827	.	.	.	.
≥4	422.767	28.782	366.354	479.181	501	105.589	294.045	707.955

DISCUSSION

COPD is characterized by progressive chronic systemic inflammation with frequent exacerbations, and malnutrition is common in the clinical course. Many factors, especially smoking and systemic inflammation induce TNF-α and neutrophils, which may cause malnutrition despite adequate nutrient intake (10). Therefore, the presence of malnutrition in COPD patients may play an important role in disease progression and symptom control. Various methods have been used to screen the presence of malnutrition in COPD patients (10). In addition, while in most of the previous studies analyzing the nutritional status of COPD patients other nutritional risk scales were used, we evaluated the nutritional status of the patients with the NRS-2002 scale in our study. As a result of the study, we found that if the NRS-2002 score is<4, the 90-day survival rate is 87.3%, the 180-day survival rate is 85.9%, and the 1-year survival rate is 74.6%. In the patients with an NRS-2002 score≥4, the 90-day survival rate is 73.9%, the 180-day survival rate is 64.3%, and the 1-year survival rate is 55.7%. The survival time of the cases in the NRS-2002<4 group was significantly higher than the cases in the NRS-2002≥4 group

In their study, Ogan et al. (11) found a significant correlation between NRS-2002 malnutrition risk assessment score and the mMRC (Modified Medical Research Council) dyspnea scale in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) C and D group patients with stable COPD, and it was determined that there was a relationship between symptom level and nutritional status of patients with COPD. In the study of Benedik et al. (12) it was observed that malnourished COPD patients had low upper arm and middle arm circumference. According to the literature, as the nutritional status deteriorated, a decrease is observed around the upper and middle arm, and the lowest values were found in patients with the highest risk of malnutrition.

Marco et al. (13) evaluated nutritional deficiencies of 118 COPD patients without exacerbation and/or who were not hospitalized according to the ESPEN definition, and included parameters such as involuntary weight loss, BMI, and fat-free mass index (FFMI). The prevalence of malnutrition was observed to be 24.6% and it was found that an increase in malnutrition was associated with the increased risk of mortality.

In their study, Chen et al. (14) found that both BMI and NRS-2002 scores were independent predictors of 1-year mortality in COPD patients with respiratory failure, but the NRS-2002 score was superior to BMI for the prediction of 1-year mortality. In the ROC analysis, they revealed that the cutoff value that can predict long-term mortality is 3 points and above for NRS-2002. It has been inferred that when the NRS-2002 score is ≥3 during admission, a COPD patient with respiratory failure is more likely to die within 1 year after discharge. In our study, the mean NRS-2002 score of the survivors was 3.36±1.16, while that of the exitus group was 3.93±1.07.

We found a significant difference between the survivors and the exitus group in terms of weight, nutritional score, number of stays in the hospital, and NRS-2002 score. Evaluation of the nutritional status of COPD patients by NRS-2002 can provide information about age and disease severity compared to BMI. Thus, NRS-2002 can comprehensively show the nutritional status of COPD patients with respiratory failure and help accurately predict their long-term prognosis.

Baumgartner et al. (15) investigated the effects of individualized nutritional support on mortality and other important clinical outcomes in a subgroup of patients with lower respiratory tract infections. They found a 25% reduction in 30-day mortality with nutritional support in patients with lower respiratory tract infections who were at nutritional risk. Evidence on nutritional support is insufficient in patients with the infection without critical illness. However, several publications are showing that nutritional support has positive effects on outcomes for patients at risk, in the general patient population (16,17).

CRP has been used for many years (18). In the study by Qu et al. (19) CRP levels of nonsurvivors in ICU were found to be significantly higher than those of survivors. As a dichotomous variant, CRP>62.8 mg/L at admission to ICU was associated with increased ICU mortality, regardless of whether the patient was septic or not. This may be related to the lack of specificity of CRP whether the patient has sepsis or not (20). Although a study claims that the assessment of serum CRP levels is not an adequate test to predict mortality in ICU patients (21), other studies showed that CRP is a suitable predictor of mortality (22,23). In our study, there was a significant difference in terms of CRP values between the survivor group and the exitus group in the 1-year mortality assessment. Also, we found significantly lower CRP

values in survivors (mean CRP 57.72 mg/L in survivors, and 85.98 mg/L in the exitus group). In our study, it was observed that the risk of death increased 1.002 times when CRP increased by 1 unit. Therefore, in clinical practice, CRP may be useful to help clinicians assess the prognosis of ICU patients.

In our study, there is a significant difference between the survivors and the exitus groups in terms of Hemoglobin and Hematocrit values. We found that the hemoglobin and hematocrit levels of the survivors were significantly higher than the exitus group.

In a study conducted by Gammelager et al. (24) in 2012, it was found that 15% of the patients had acute kidney damage during admission to the ICU. An increase by two times in 30-day mortality was identified in patients who were in the acute kidney injury group during admission to the ICU. Relative mortality in patients with acute kidney injury was found to be associated with 33-64% increased mortality in the 31-365 days following the admission to the ICU. The relationship between comorbidities and mortality was investigated in our study, there was a statistically significant relationship between Acute or Chronic renal disease and mortality. In addition, BUN values were found to be significantly higher in the exitus group. In all large studies involving large numbers of ICU patients, an increase in short/medium term mortality, and in-hospital mortality for patients with acute kidney injury during admission to the ICU or during their stay in the ICU was reported. In these studies, the relative risk of in-hospital mortality increased by 1-1.6 times for patients with acute kidney injury and between 1.6 and 4.1 times for patients with acute renal failure (25,26).

Scoring systems [such as APACHE II; Simplified Acute Physiology Score II (SAPS II) and Multiple Organ Dysfunction Score (MODS)] are used to determine the severity of the disease, response to treatment, expected mortality rates, and intensive care performance of patients followed up in intensive care units (27). In their study comparing the worst APACHE II scores at first admission and in the first 24 hours, Ho et al. (28) found that the expected mortality was 15.5% and 19.3% respectively, and the actual mortality was 16.3% . They stated that the sensitivity and specificity of the APACHE II score determined at the first admission were decent and that it could be used for intensive care patients without trauma. We evaluated the patients with the APACHE II scoring system during their admission to the ICU. In line with the literature, we found a significant difference between the APACHE II scores and the number of admissions to the ICU after discharge between the two groups. The number of admissions to the emergency room after discharge and APACHE II score levels of the exitus group were significantly higher than those of the survivors. Studies are suggesting that the 'discharge APACHE II score' outperforms the 'admission APACHE II score', for readmission to the hospital (29).

Limitations

Our study was carried out in a single center and designed as a retrospective. In addition, the patients were evaluated with a single nutritional assessment method at admission. The NRS-2002 score is the nutritional risk screening tool recommended by ESPEN and is more suitable than most other available methods due to its simplicity, applicability, and non-invasive nature. However, as NRS-2002 contains subjective content, the outcome of the evaluation is somewhat dependent on the evaluators. For this reason, we consider that an experienced evaluator is needed. The strong aspect of our study is, the NRS-2002 scoring was applied to the patients by experienced dietitians and intensive care physicians to avoid subjectivity and bias. Also, The COPD exacerbations are closely affected by seasonal changes. We include patients in 1 year to avoid seasonal bias.

CONCLUSION

We demonstrated that high NRS-2002 scores, high CRP levels, and prolonged stay in the hospital were associated with the mortality risk. Combining the NRS-2002 tool with CRP and prolonged stay in the hospital can produce more accurate results in evaluating a patient's nutritional status in clinical practice and help make predictions about the patient's prognosis. More studies may evaluate the nutritional status of COPD patients, not only in hospitals but also in outpatient clinics.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Keçiören Education and Training Hospital Clinical Studies Ethics Board (Date: 14.09.2021 Decision No: 2012-KAEK-15/2355).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Effect of SARS-CoV-2 pandemic on breast cancer stage at diagnosis

Murat Bulut Özkan, Veysel Barış Turhan, Murat Baki Yıldırım, Ramazan Topçu

Hitit University, Erol Olçok Training and Research Hospital, General Surgery Clinic, Çorum, Turkey

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ABSTRACT

Objective: We aimed to research the effects of the COVID-19 pandemic on breast cancer stages at the time of diagnosis.

Material and Method: The data of female patients over 18 who underwent breast surgery and sentinel lymph node sampling for malignancy between 01.06.2019 and 31.11.2019 with between 01.06.2020 and 31.11.2020 were analyzed. Patients were divided into two groups as before and during the pandemic.

Results: Data of 55 patients in total were reached, of which 31 were diagnosed before the pandemic and 24 after the pandemic. There is no significant difference between the two groups in terms of age. Average tumor size is 3.42±2.00 cm, and 18 patient (32.7%) has positive sentinel lymph node biopsy (SLNB). In before pandemic group (Group 1) SLNB positivity rate is only 25.8% (n=8) but in during pandemic group (Group 2) this rate reaches 41.7% (n=10), but this is not statistically significant(p=0.214). While the tumor size of the patients in Group 1 was 3.35±2.25 cm, it was 3.51±1.67 cm in Group 2. Still, no statistically significant difference was observed (p=0.141).

Conclusion: As a result of our study, although statistically insignificant, an increase in tumor sizes and positive lymph node numbers was detected. We predict that statistically significant results will be obtained in studies with a larger number of cases.

Keywords: COVID-19, SARS-CoV2, breast cancer, SLNB, prognosis

INTRODUCTION

The SARS-CoV-2 disease was first reported to the World Health Organization (WHO) on 31 December 2019 in Wuhan City, Hubei Province, China (1). WHO defined this disease as COVID-19 on 11 February 2020 (2). During the pandemic, especially at the beginning of the quarantine, there was a significant slowdown in clinics that could make the oncological diagnoses and organize treatments, and only emergency medical services were resumed (3). Lai et al. (4) found a 60% reduction in patients receiving chemotherapy and a 76% reduction in referrals for early diagnosis. It has been shown that cancer-related deaths increase in this process (5). Thus, cancer-related deaths may have risen since cancer patients caught COVID-19, as well as the disruption of treatment services and delays in diagnosis during the pandemic. While emerging vaccines show great promise, not everyone's access to vaccines and the emergence of new variant viruses indicate that it will take some time before health services, including cancer services, return to pre-pandemic capacity and cancer prevention services. Also, it has been shown that patients with co-morbidities are more prone to COVID-19, and in this population, this infection is more hazardous (6,7).

Breast cancer is the most commonly diagnosed cancer worldwide. 2,3 million new cases are diagnosed annually (6). If breast cancer is caught at an early stage, a significant survival advantage is provided. While the one-year survival rate of breast cancer diagnosed in Stage 1 is 100% in recent studies, and this rate drops to 66% for Stage 4. For this reason, screening tests are carried out in many countries. Screening programs reduce breast cancer mortality by 20% (7). In addition, early diagnosis and treatment provide good aesthetic results, reduce the need for adjuvant therapy, provide an early return to work, and improve the quality of life.

During the pandemic, there has been a prominent decrease in hospital admissions and delays in diagnosis and treatment. In addition, some countries had to postpone outpatient services and screening programs due to the overload in their health systems during the COVID-19

Corresponding Author: Murat Bulut Özkan, bulutozkan@gmail.com

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pandemic. Besides, national screening programs in many countries, including Turkey, have been completely suspended for 1-6 months (8). Even in countries where screening services are being continued, attendance has been reported to have decreased by almost 50% (9).

Our study aims to evaluate the effect of suspension of screening and outpatient services on the stage of breast cancer at diagnosis during the COVID-19 pandemic.

MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Non-Interventional Research Ethics Committee (Date: 30.04.2021, Decision No: 2021-66) for our retrospective study. Our study was carried out under the principles of the Declaration of Helsinki and an informed consent form was signed by all patients. Between these dates, demographic data, sentinel lymph node positivity status, number of lymph nodes removed, tumor sizes, and whether they received neoadjuvant treatment were retrospectively questioned from patient files and the hospital data systems.

Study Group

This study was conducted on female patients over 18 years of age who underwent breast surgery and sentinel lymph node biopsy (SLNB) due to malignancy in the General Surgery Clinic of Hitit University Erol Olçok Training and Research Hospital between 01.06.2019 and 31.11.2019 with 01.06.2020 and 31.11.2020.

While determining the dates of patient selection, attention was paid to the absence of April and May, when quarantine was most intense, and elective surgeries were suspended, and patients diagnosed within six months starting from June were included in the study. The dates for screening the other group of patients (Group 1 or before the pandemic group) were determined considering the projection of this time interval to the pre-pandemic period. Fifty-five patients were found to be eligible for the study.

Exclusion criteria were defined as patients under 18 years of age, non-operated breast cancer patients, patients whose final pathology report was not reported as breast cancer, patients whose data could not be accessed, and patients who did not want to be included in the study. A total of 101 patients were examined, and 55 patients who met the criteria were included in the study.

Study Protocol and Definitions

Preoperative diagnosis was obtained by core needle biopsy or stereotactic biopsy. In addition, data on previous administration of neoadjuvant chemotherapy were collected from clinical notes. The surgical procedure was performed as breast surgery (breast-conserving surgery or mastectomy) and SLNB in all patients.

Breast surgery includes breast-conserving surgery or mastectomy, depending on tumor size, breast size, and patient's choice. Axillary assessment; SLNB was performed in patients without clinical or radiological evidence of pathological lymph nodes. Afterward, axillary lymph node dissection (ALND) was performed in patients with SLNB positivity.

Patients with clinically or radiologically pathological lymph nodes or findings suggestive of locally advanced breast cancer were referred to neoadjuvant therapy.

SLNB was performed by applying a five cc patent blue injection to the periareolar tissue and pectoral fascia. There are studies showing that periareolar injection for SLNB is superior to peritumoral injection due to its simplicity and high success rate in SLN detection (10). For deeply located tumors, 0.5 ml peritumoral injection is recommended (11). Approximately 10 minutes after the application, the lymph nodes stained with an axillary incision were removed and sent for frozen section examination. Data obtained from surgical specimens were included in the study. Tumor maximum diameters were reported as tumor size in centimeters.

Patients who had breast surgery during the pandemic period were evaluated in our study and considered the during pandemic group (Group 2). These patients were compared with patients who had breast surgery in the same period of the previous year, defined as the before the pandemic group (Group 1). These dates were determined to be correlated with the dates when non-emergency surgery cases were started to be cared for at the outpatient level in Turkey.

Statistical Analysis

All statistical analyzes were performed using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA). Categorical variables, sentinel lymph node positivity, and neoadjuvant treatment status were reported as numbers and percentages. The numerical variables, age and tumor size, were reported as mean value ± standard deviation and median value in parentheses. The number of lymph nodes removed was reported as median value and minimum and maximum values in parentheses. Relationships between variables were investigated with Pearson and Spearman correlation coefficients. The statistical difference of categorical variables between the groups was evaluated by using the Chi-Square test. Data normal distribution in numerical data were evaluated with the Shapiro Wilks test. The Mann-Whitney U test was used in accordance with the data distribution for the number of lymph nodes removed, tumor size, and age comparisons between the two groups. For the statistical significance level, $p<0.05$ was accepted.

RESULTS

When the mean age of 55 patients constituting the whole group was examined, it was found to be 56.29±12.84 years. SLNB was positive in 18 (32.7%) of 55 patients. The mean tumor size removed from the patients was 3.42±2 cm (**Table**).

To determine the effect of the pandemic on breast cancer stage at the time of diagnosis, the patients were divided into two groups as "before the pandemic" (Group 1) (n=31) and "during pandemic" (Group 2) (n=24) and it was investigated whether there was a significant difference between the parameters. The mean age of the patients in Group 1 was 57.16±12.30 years, the mean age of the patients in Group 2 was 55.17±13.70 years; no statistically significant difference was observed (p=0.575). Three (9.7%) of the patients in Group 1 were referred to neoadjuvant therapy, compared to 4 (16.7%) in Group 2. Despite the difference between the percentages of patients referred to neoadjuvant therapy, no statistically significant difference was observed (p=0.686). While the mean tumor size of the patients who underwent surgery in the pre-pandemic period was 3.35±2.25 cm, it was 3.51±1.67 cm in the pandemic period. Although an increase in tumor size was detected between the two groups at the time of diagnosis, this difference was not sufficient to affect staging and was not statistically significant (p=0.141). Positive SLNB rate was found to be 25.8% (n=8) in patients in Group 1, while this rate increased to 41.7% (n=10) in Group 2, but no statistically significant difference was observed (p=0.214).

DISCUSSION

The rapid spread of the SARS-Cov 2 virus has caused the pandemic. Due to the fast human-to-human transmission, many countries continue to impose severe restrictions to limit the spread. These restrictions have changed our daily routines and caused reorganizations in health practices. In addition, non-emergency medical services were suspended during this period. Routine oncology preventive activities also slowed down, especially at the beginning of the pandemic (3,12). In our study, the effect of the pandemic on the clinical staging of breast cancer at the time of diagnosis was investigated.

Although breast cancer is the most common cancer in society and one of the most common causes of cancer-related deaths in women, recent improvements in prognosis have been observed due to the possibility of early diagnosis in breast cancer and the implementation of screening programs (13-15) . One of the factors that most affect survival is the stage of breast cancer (16). It has been reported that the ten-year overall survival and disease-free survival rates of breast cancer patients according to the stages are 67-88% and 70-75%, respectively (17). Local recurrence rates in these patients are between 8-19% (18).

However, with the COVID-19 pandemic, screening tests have been interrupted due to the burden on the health system. In the center where the study was conducted, it was observed that the number of outpatient clinic applications and the number of mammographies performed due to breast complaints during the COVID-19 pandemic decreased significantly compared to the previous year. For this reason, clinicians have been concerned about the progression of the breast cancer stage in the population. Unfortunately, there are no extensive studies on this subject in the literature. Tumor size, lymph node positivity, and distant organ metastasis are effective in breast cancer staging (19). Distant organ metastasis was not detected in any of the patients included in the study at the time of the study. For this reason, tumor size and SLNB positivity were examined for comparison in our study.

Despite the suspension of breast cancer screening, we did not observe an increase in T stages. However, the mean mass size increased from approximately 3.3 cm to 3.5 cm. The reason for this result may be the low number of patients and the relatively short lockdown time. Although the increase in size is not statistically significant, this increase is essential for the prognosis of the disease (20). Studies are showing that tumor size has a direct effect on survival (21). In addition, studies have shown that tumor size is correlated with positive lymph node numbers (20,22,23). Therefore, Increasing the number of positive lymph nodes and tumor size worsens the prognosis. However, these two clinical outcomes are independent of each other. For example, the prognosis worsens with or without a positive lymph node as the tumor size increases (20,24).

Table.

Variables		All Patients (n=55)	Group 1 (before the pandemic) (n=31)	Group 2 (during pandemic) (n=24)	Statistical Significance
Age (Years)		56.29±12.84 (58)	57.16±12.30 (59)	55.17±13.70 (56.5)	0.575*
Neoadjuvant Chemotheraphy		7 (%12.7)	3 (%9.7)	4 (%16.7)	0.686†
Tumor Size (Centimeters)		3.42±2.00 (3)	3.35±2.25 (2.5)	3.51±1.67 (3.05)	0.141*
Sentinel Lymph Node Count		1 (1-6)	1 (1-5)	1.5 (1-6)	0.380*
Sentinel Lymph Node Status	Negative	37 (%67.3)	23 (%74.2)	14 (%58.3)	0.214*
	Positive	18 (%32.7)	8 (%25.8)	10 (%41.7)	

* Mann-Whitney U with mean±standard deviation(median), † Chi-square test

Lymph node metastasis is one of the most important prognostic factors in breast cancer (20,25). When we look at SNLB positivity in our study group, it was observed that it increased from 25,8% to 41,7%, although it was not statistically significant. This increase is one of the most drastic effects of the pandemic. The study compares two periods of 6 months. Although this period was relatively short, it caused delayed diagnosis in breast cancer patients and also increased both size and lymph node positivity.

Our study contains deficiencies due to the nature of retrospective studies. It has limitations as the lockdown period is relatively short, the number of patients is small, it was performed in a single-center, and some patients did not want to participate in the study. However, it contains valuable information in terms of the fact that it is a study that emphasizes the importance of cancer screening. Breast cancer can be cured if diagnosed in the early stages, and that a critical follow-up process is noted in pandemic conditions other than emergency surgeries. As far as we know, there is no further research on the effects of the pandemic on the stage of breast cancer.

CONCLUSION

As a result, we believe that breast cancer is one of the diseases that should not be followed up during epidemic periods such as COVID-19, which is rare and affects the whole world, and that society should be informed more. By providing appropriate protection conditions, breast cancer screening and diagnostic evaluations should not be disrupted. Our study showed that even in this short period, there was an increase in tumor sizes and positive lymph node counts. This information is of great importance for more extended lockdown periods.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Non-Interventional Research Ethics Committee (Date: 30.04.2021, Decision No: 2021-66).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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The relationship of obstructive sleep apnea risk with the disease severity and clinical parameters in COPD population

Ali Onur Keleş[1], Sezgi Şahin Duyar[1], Funda Aksu[2], Selma Fırat[2]

[1]University of Health Sciences, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Pulmonology, Ankara, Turkey
[2]University of Health Sciences, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Sleep Disorders Center, Ankara, Turkey

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ABSTRACT

Aim: Obstructive sleep apnea syndrome (OSAS) and chronic obstructive pulmonary disease (COPD) have common pathophysiological mechanisms affecting the prognosis of each other. This study aims to investigate the relationship between the presence of OSA risk and the severity of COPD and to determine the possible clinical features for OSA risk for COPD patients.

Material and Method: The patients (n=181) who applied to the outpatient clinics of pulmonology between September - November 2019 with the diagnosis of COPD, were analyzed cross-sectionally. Demographic features, anthropometric measurements, comorbidities, smoking status, and severity of dyspnea, respiratory functions, and exacerbation frequency in the last year were evaluated. All patients were questioned with the Epworth sleepiness scale (ESS) for detecting excessive daytime sleepiness (EDS), and the STOP-Bang for determining the risk of OSA.

Results: The rate of diabetes, waist and hip circumference measurements, median ESS score, and EDS ratio were found to be higher in patients with moderate/high OSA risk when compared to patients with low OSA risk. In the multivariate regression model; lower oxygen saturation (OR: 0.83; p=0.007) and higher ESS score (OR=1.28; p<0.001) were determined as independent risk factors affecting the OSA risk to be moderate/high.

Conclusion: Low oxygen saturation, accompanying diabetes, high ESS score and, high waist-hip circumference stand out as useful factors in determining OSA risk in the COPD population. However, OSA risk was found to be the same among all COPD stages. We suggest that all COPD patients should be questioned for OSA risk regardless of the stage.

Keywords: Obstructive sleep apnea syndrome (OSAS), chronic obstructive pulmonary disease (COPD), Epworth sleepiness scale (ESS), STOP-Bang survey

INTRODUCTION

It is known that chronic obstructive pulmonary disease (COPD) has many comorbidities affecting prognosis. Obstructive sleep apnea syndrome (OSAS) which is one of the common comorbidities, is affected by various clinical and pathophysiological factors associated with COPD. According to epidemiologic studies, OSA can be present in about 10 to 15% of patients with COPD (1,2). Hypoxemia and inflammation are the main factors affecting the pathology and prognosis of both diseases. The overlap of OSA and COPD results in more profound nocturnal hypoxemia especially during rapid eye movement (REM) sleep and cardiovascular comorbidities (3,4).

Peripheral fluid retention shifting rostral during sleep, corticosteroid therapy which may weaken pharyngeal muscles and cigarette smoking causing inflammation in the upper airway, facilitate the collapsibility of the upper airway in COPD (3). A phenotypic tendency for the coexistence of OSA was observed for the patients with chronic bronchitis while hyperinflation associated with COPD was found to be protective against upper airway collapse in the predominant emphysema phenotype (5-7). Besides, cachexia which is seen during the end stages of COPD might decrease the likelihood of coexisting OSA in this population. The alterations in pathophysiological changes in the stages and phenotypes of COPD can affect the prevalence of OSA. Furthermore, OSA has a significant effect on the survival of COPD patients. It may increase the lower airway inflammation and worsen respiratory failure in COPD (1). In some studies, it is associated with daytime oxygen desaturation, hypercapnia, and poor quality of life in patients with COPD (2,8,9).

Corresponding Author: Sezgi Şahin Duyar, drsezgisahin@gmail.com
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Screening for OSA risk is an important part of the clinical evaluation of patients with COPD. This study was conducted to find the relationship between the presence of obstructive sleep apnea (OSA) risk and the severity of COPD and to reveal the clinical findings which can determine the intermediate/high OSA risk in COPD patients.

MATERIAL AND METHOD

The study was approved by the Keçiören Training and Research Hospital Clinical Research Ethics Committee (Date: 11.09.2019, Decision No:2012-KAEK-15/1938). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

In this study; 181 patients aged between 40-75 years, who were admitted to the outpatient clinics of pulmonology between September 1st, and November 31st, 2019 with the diagnosis of COPD, were analyzed cross-sectionally. Only the patients who signed informed consent were enrolled in the study. Patients with congestive heart failure, chronic renal disease, psychiatric or neurological diseases, shift work, and patients on positive airway pressure treatment due to respiratory failure were excluded.

The diagnosis of COPD and the evaluation of disease severity was based on the global initiative for chronic obstructive lung disease (GOLD) 2019 criteria (10). Combined COPD assessment including symptom severity and exacerbation history was used.

Measurements

Demographic features [age, gender], anthropometric measurements, comorbidities, smoking status, and severity of dyspnea according to the modified medical research council (mMRC) scale (11), respiratory functions, and exacerbation frequency in the last year were evaluated.

For anthropometric evaluation height [m], weight [kg], neck, waist, and hip circumferences (cm) were measured with a tape measure. Weight was measured with light clothing and without shoes. The height was measured on bare feet with the thin rod parallel to the floor that touched the head during deep inspiration while standing upright. The body-mass index (BMI) was calculated as weight [kg] divided by the square of height [m²]. Neck circumference (NC) was measured at the level of the cricothyroid membrane in a standing position. Waist circumference (WC) was measured midway between the lower rib and the iliac crest, and hip circumference at the level of the widest circumference over the great trochanters during upright position at the end of a gentle expiration. Pulse oximetry was used for measuring oxygen saturation (SpO_2) on room air at rest.

Spirometry was performed under the American Thoracic Society (ATS)/European Respiratory Society (ERS) standards (12). Forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC values were obtained with the forced expiration curve. The severity of airway obstruction was based on the level of post-bronchodilator FEV1% of the predicted value (10). The airway obstruction was classified as mild, intermediate, severe, and very severe according to cut-off values of FEV1 80%, 50%, and 30% respectively. All patients were questioned with the Epworth sleepiness scale (ESS) for detecting excessive daytime sleepiness (EDS), and the STOP-Bang for determining the risk of OSA. Both questionnaires were validated in Turkish (13,14). EDS was defined when the total score was 10 or more on ESS. If the score was ≤2 on the STOP-Bang questionnaire the risk for OSA was assumed as low. The patients with a score >2 were grouped as intermediate/high OSA risk.

Statistical Analysis

For the statistical evaluation, the Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., Chicago, IL) for Windows 23 was used. The distribution of data was evaluated by the Kolmogorov-Smirnov test. For random distribution, the median [25th percentile (P25) and 75th percentile (P75)] was displayed whereas mean±standart deviation was used for normal distribution. The results from qualitative data were shown as numbers and percentages. The Chi-Square test or Fisher Exact test was used to compare qualitative data. The Mann-Whitney U test (for random distribution) or independent sample T-test (for normal distribution) were executed for the comparisons between the groups of numerical variables. Correlations between numerical data were evaluated by Spearman correlation analysis, and the correlation between categorical variables was determined by the point biserial correlation. Multivariate regression analysis was used to determine the independent risk factors of the STOP-Bang survey risk score and Epworth Sleepiness Scale Score. Data with random distribution was emulated to a normal distribution with logarithmic transformation. Multivariate logistic regression analysis was used to determine the independent risk factors of OSA risk and daytime sleepiness. In statistical analysis, the p-value <0.05 was considered significant.

RESULTS

The patients enrolled in the study (n=181) consist of 140 (77.3%) males and 41 (22.7%) females, aged between 40-75 years. The mean age of the patients was 62.1±8.8 years,

the average BMI level was 26.8±5.4 kg/m², and the average neck circumference was 40.6±3.5 cm. It was determined that 32% (n=58) of the patients were active smokers and 49.2% (n=89) had quited smoking. The median smoking time was 40 packs/year. The median disease duration of the patients who applied to the outpatient clinic for COPD was 4 years. According to the combined COPD assessment, stated on GOLD 2019, 37% (n=67) of the patients were classified in the high-risk group (GOLD C and GOLD D) for exacerbation and symptom burden. As to spirometric grade, approximately half of the patients (n=93, 51.4%) had GOLD 3-4 grade of airflow limitation (FEV1<50%). The presence of hypertension was declared by 30.4% (n=55) of patients and diabetes mellitus was declared by 11% (n=20) of the patients.

In our study, the ratio of patients with intermediate/high OSA risk was 69.6% (n=126). The median ESS score was 4 and the rate of EDS was found to be 30.4% (n=55).

As shown in **Table 1**, waist circumference and hip circumference measurements in this COPD population were also found to be significantly higher in the group with intermediate /high OSA risk (p<0.001). The rate of diabetes (14.3% and 3.6%; p=0.040), median ESS score (7.5 and 2, respectively; p<0.001), and EDS ratio (42.1% and 3.6%, respectively; p<0.001) were found to be higher in patients with intermediate/high OSA risk when compared to patients with low OSA risk. Besides, SpO_2 (92.3±4.3 and 94.2±2.3; p<0.001) and FVC (2,3±0.8 and 2.6±0.8; p=0.050) were significantly low in patients with intermediate/high OSA risk. However, the other clinical parameters including the mMRC scale, GOLD stages and exacerbation/hospitalization history did not differ significantly between OSA risk groups (**Table 1**).

The previous analysis indicated that waist circumference, hip circumference, FVC, SpO_2, ESS score, and EDS could be possible risk factors associated with intermediate/high OSA risk. In the multivariate logistic regression model in which these possible risk factors are included, SpO_2 (OR: 0.83; p=0.007) and ESS score (OR=1.28; p<0.001) were determined as independent clinical factors affecting the intermediate// high level of OSA risk (**Table 2**).

Table 2. Multivariate regression analysis for OSA risk

Variables	OR	95% CI		p
		Lower limit	Upper limit	
OSA risk (intermediate/high vs low)				
SpO_2 (%)	0.83	0.72	0.95	0.007
ESS	1.28	1.16	1.41	<0.001
Nagelkerke R2:0.331; p<0.001				

CI: Confidence interval, ESS: Epworth sleepiness scale OR: Odds ratio, SpO_2:oxygen saturation by pulse oximetry

Table 1. Demographic and clinic parameters according to the OSA risk group

Parameters	OSA Risk		p
	Low (n=55)	Intermediate/ High (n=126)	
Age (years)	61.8±9.4	62.3±8.6	0.714
Gender, n (%)			
Male	42 (76.4)	98 (77.8)	0.848
Female	13 (23.6)	28 (22.2)	
BMI (kg/m²)	24.8±3.8	27.7±5.8	<0.001
Neck circumference (cm)	39.0±2,6	41.2±3,6	<0.001
Waist circumference (cm)	93.0±9.7	99.2±13.8	0.001
Hip circumference (cm)	97.6±10	104.6±12.9	<0.001
Cigarette smoking (pack/years)	40 (15-50)	40 (16-60)	0.208
Never-smoked, n (%)	10 (18.2)	24 (19.0)	0.976
Quitted, n (%)	28 (50.9)	61 (48.4)	
Active-smoker, n (%)	17 (30.9)	41 (32.5)	
Comorbidities n (%)	6 (10.9)	62 (49.2)	<0.001
HT n (%)	3 (5.5)	52 (41.3)	<0.001
DM n (%)	2 (3.6)	18 (14.3)	0.040
Duration of COPD	4 (0.5-9)	4 (1-10)	0.365
PFT			
FVC (L)	2.6±0,8	2.3±0,8	0.050
FEV 1 (L)	1.6±0.7	1.4±0.6	0.088
FVC, %	68.6±22.6	62±16.2	0.057
FEV 1, %	54.6±21.2	49±15.6	0.085
FEV1/FVC	61.0±6.8	60.8±8.3	0.837
SpO_2, %	94.2±2.3	92.3±4.3	<0.001
Airflow limitation, n (%)			
GOLD1 (FEV1≥80%)	6 (10.9)	7 (5.6)	0.430
GOLD2 (50%≤FEV1<79%)	25 (45.5)	50 (39.7)	
GOLD3 (30%≤FEV1<%50%)	20 (36.4)	58 (46.0)	
GOLD4 (FEV1<30%)	4 (7.3)	11 (8.7)	
mMRC scale, n (%)			
mMRC<2	20 (36.4)	34 (27.0)	0.220
mMRC≥2	35 (63.6)	92 (73.0)	
GOLD 2019			
A	17 (30.9)	26 (20.6)	0.338
B	22 (40)	49 (38.9)	
C	3 (5.5)	7 (5.6)	
D	13 (23.6)	44 (34.9)	
Exacerbations ≥2/past year, n (%)	14 (25.5)	46 (36.5)	0.171
Hospitalizations ≥1/past year, n (%)	5 (9.1)	19 (15.1)	0.345
ICU admissions ≥1/past year, n (%)	0	4 (3.2)	0.432
ESS score	2 (0-4)	7.5 (3-11)	<0.001
EDS, n (%)	2 (3.6)	53 (42.1)	<0.001

The results were shown as n (%), mean ± standard deviation or median (25^{th}-75^{th} percentile) BMI: body-mass index, COPD: chronic obstructive pulmonary disease DM: diabetes mellitus, EDS: excessive daytime sleepiness, ESS: Epworth sleepiness scale, FEV1: Forced expiratory volume in one second, FVC: forced vital capacity, GOLD: global initiative for chronic obstructive lung disease HT: hypertension, ICU: intensive care unit, mMRC: modified medical research council, SpO_2:oxygen saturation by pulse oximetry

Our results revealed that STOP-Bang score had an intermediate positive correlation with waist circumference (r=0.429; p<0,001), hip circumference (r=0.409; p<0.001) and ESS score (r=0.457; p<0.001). The presence of DM, COPD duration, FVC(L), FEV1(L), FVC%, SpO_2, GOLD 2019 ABCD staging, airway obstruction, and mMRC dyspnea scale showed a weak correlation with STOP-Bang score (**Table 3**). These factors associated with the STOP-Bang score were included in the multivariate linear regression model in which SpO_2(β±SH: -0.09±0.03; p=0.007) and log (ESS) (β±SH: 0.14±0.02; p<0.001) outshined as independent factors affecting the risk score (**Table 4**).

Table 3. The results of correlation analysis between STOP-Bang score and the demographical-clinical parameters

Parameters	STOP-Bang score	
	r	p
Age (years)	0.083	0.268
Gender	0.001	0.986
Waist circumference (cm)	0.429	<0.001
Hip circumference (cm)	0.409	<0.001
Cigarette smoking (pack/years)	0.075	0.366
DM	0.286	<0.001
Duration of COPD	0.178	0.017
FVC (L)	-0.184	0.014
FEV1(L)	-0.159	0.034
FVC(%)	-0.173	0.020
FEV1(%)	-0.138	0.065
FEV1/FVC	0.049	0.517
SpO_2(%)	-0.228	0.002
GOLD 2019 (ABCD stages)	0.281	<0.001
The severity of airflow limitation	0.149	0.045
mMRC scale	0.255	0.001
ESS score	0.457	<0.001

COPD: chronic obstructive pulmonary disease DM: diabetes mellitus, EDS: excessive daytime sleepiness, ESS: Epworth sleepiness scale FEV1: Forced expiratory volume in one second, FVC: forced vital capacity, GOLD: global initiative for chronic obstructive lung disease, ICU: intensive care unit, mMRC: modified medical research council SpO_2: oxygen saturation by pulse oximetry

Table 4. Multivariate regression analysis for STOP-Bang score

Variables	OR	%95 CI		p
		Lower limit	Upper limit	
Log (STOP-Bang score)	β±SH			
SpO_2 (%)	-0.09±0.03	-0.16	-0.03	0.007
log (ESS)	0.14±0.02	0.10	0.18	<0.001
		R2: 0.285; p<0.001		

CI: Confidence interval, ESS: Epworth sleepiness scale OR: Odds ratio, SpO_2: oxygen saturation by pulse oximetry, β±SH: regression coefficient ± standard error

DISCUSSION

The overlap of OSA and COPD has some common factors affecting the pathophysiology and prognosis of each other. It is important to reveal the factors determining OSAS risk in COPD. The common factors such as age, gender, and smoking, may not provide clinical benefit in determining the probability of OSA. It may be speculated that especially advanced COPD with altered upper airway dynamics, respiratory pattern, and comorbidities may have different predictors from the general population (15). Approximately half of our study group consisted of COPD patients with mild/moderate airway obstruction and two-thirds of the population was with GOLD A-B representing the low-risk group for exacerbations. In this cohort of COPD patients, it was found that nearly 70% of the patients had moderate/high risk for OSA. OSA prevalence in COPD was reported between 2.9-66% in different studies (2,16,17). Sharma et al. (18) reported the prevalence of high risk for OSA according to the Berlin Questionnaire as 55.2% in obstructive airway diseases. Oppositely, polysomnographic data of The Sleep Heart Health Study and Bednarek et al. (19) claimed no risk for mild obstruction (2). However, neither the degree of the airflow limitation nor the stage of COPD seemed to affect the OSA risk in our study group.

A recent study underlined that hypertension which is a component of the STOP-Bang questionnaire, could not be shown as an indicator of OSA in moderate to severe COPD. The authors recommended the interrogation of cardiovascular events, including stroke, myocardial infarction, or peripheral vascular disease for OSA risk (15). According to our results, the presence of diabetes may be a clue for the OSA-COPD overlap. Similarly, in the study of Steveling et al. (17) in which nocturnal polygraphy was used, the frequency of diabetes was higher in patients with the overlap syndrome.

The BMI threshold for the STOP-BANG is >35 kg/m² which is more than the average BMI (26.8 kg/m²) of our study group. Although the average BMI of the intermediate/high-risk group was also found to be below the threshold, it is statistically higher than the low-risk group. On the other hand, the age threshold of 50 years might have increased the likelihood of high OSA risk in this elderly population with a mean age of 62.1 with male predominancy. But the gender distribution and mean age of the low-risk group were found to be statistically the same as the intermediate/high-risk group.

We showed that the ESS score correlates well with the OSA risk. However, it is known that the poor sleep quality in moderate/severe COPD obstacles the prediction of OSA with ESS (15,16,20). The tiredness and daytime sleepiness may be attributed to either the poor sleep quality in COPD or the accompanying OSA. Eventually, the polysomnographic evaluation is needed for the differential diagnosis. We used the STOP-Bang questionnaire in this study because STOP-Bang was found to be associated with OSA in COPD (15). But our results must be confirmed with the polysomnographic data, the lack of which is the major limitation of this study. Schreiber et al. (21)

published polysomnographic data from a pulmonary rehabilitation clinic comprising 190 COPD patients of whom 45% were diagnosed as moderate/severe OSAS. They also claimed that BMI and ESS may not be as reliable as in the general population for OSA risk assessment in a subgroup of patients with COPD.

In a Swiss cohort (17), BMI and smoking history were claimed as the only clinical predictors for OSA but other anthropometric parameters like the circumference of the neck, waist, or hip were not mentioned in this study. Contrary to the correlation between large neck circumference and OSA in the general population (22,23), it is reported that advanced COPD patients with neck circumference <42cm are also prone to have OSA (15). The severity of OSA is particularly associated with abdominal obesity, and an increase of 13-15 cm around the waist or hip increases the risk of OSA 4 times (24). These findings are also compatible with the COPD cohort in the study of Turcani et al. (25). In our study, waist and hip circumference were found to be higher in the medium/high-risk OSA group compared to the low-risk OSA group.

The overlap of COPD-OSA may cause more profound nocturnal hypoxemia than those with OSA alone (4). According to the multivariate regression model; a lower percentage of oxygen saturation (OR: 0.83; p=0.007) and higher ESS score (OR=1.28; p<0.001) were determined as independent risk factors affecting the OSA risk and STOP-BANG questionnaire score. Our study pointed out that daytime SpO_2 may be a possible *Candida*te for OSA risk assessment. In a study by Little et al. (26), it is stated that stable COPD patients with daytime arterial oxygen saturation of hemoglobin (SaO_2) ≤93% are more likely to have nocturnal oxygen desaturation. In contrast to our results, STOP-BANG was not associated with ESS in a study involving advanced COPD patients. Milder COPD patients are likely to have fewer EDS related to respiratory insufficiency. It can be expected that a stage-dependent relationship between ESS and OSA risk exists.

As to the limitations of the study, first, we could not perform polysomnography/polygraphy for the patients due to economic issues. However, the current recommendations that concern just the number of respiratory events for scoring PSG can also be insufficient to determine the real burden of breathing disorders during sleep for obstructive lung disease. The parameters including the duration of the respiratory events and the severity of the hypoxemia during sleep must be investigated for a better perception of OSA-COPD overlap. Second, the data about the comorbidities were based on patients' declarations and previous prescriptions. Therefore, we could have some missing data due to memory factor and lack of objective tests for comorbidities.

CONCLUSION

In this study, it was revealed which clinical findings other than commonly used factors such as body-mass index can determine the intermediate/high OSA risk in COPD patients. Our results showed that low oxygen saturation, accompanying diabetes, high ESS score, and the high waist-hip circumference can be useful factors in differentiating patients with intermediate/high OSA risk in the COPD population. Furthermore, no difference in OSA risk was detected among all COPD stages according to GOLD. We suggest that all COPD patients should be questioned regardless of the stage in terms of OSA risk and the patients with the aforementioned characteristics should be directed to sleep clinics for polysomnography.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Keçiören Training and Research Hospital Clinical Research Ethics Committee (Date: 11.09.2019, Decision No:2012-KAEK-15/1938).

Informed Consent: All patients signed the free and informed consent form for the usage of their data.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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The correlations between pulmonary function tests and polysomnographic parameters in overlap syndrome

Sezgi Şahin Duyar[1], Deniz Çelik[2], Selma Fırat[1]

[1]University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Sleep Disorders Center, Ankara, Turkey
[2]Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Pulmonology, Antalya, Turkey

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ABSTRACT

Aim: This study aims to reveal the relationship between Pulmonary Function Tests (PFTs) parameters and polysomnographic parameters. It aims to determine the guiding values in treatment selection, with the hypothesis that easily accessible PFTs parameters can be useful in clinical evaluation for patients with restrictive or obstructive type disorders.

Material and Method: One hundred and forty-six patients with obstructive and/or restrictive pulmonary dysfunction who underwent polysomnography in the sleep clinic of our hospital between June 2019 and December 2019 were included in the study. Polysomnography (PSG) parameters and PFTs results were obtained. Age, gender, body mass index (BMI), Epworth Sleepiness Scale (ESS) score, PFTs parameters, apnea-hypopnea index (AHI), nocturnal oxygen saturation, tolerable positive airway therapy modality, and pressures were recorded.

Results: Of 146 patients 34.9% were women and most (92.5%) had an obstructive disorder in PFTs. Of the patients with the obstructive disorder, 71 were being followed up with a diagnosis of chronic obstructive pulmonary disease (COPD) and 64 with a diagnosis of asthma. Interstitial lung disease was observed in 5 out of 11 cases (7.5%) with restrictive type disorder, and obesity resulted in restrictive disorder for the remaining 6 cases. Simple snoring was observed in 5.5%. Mild OSAS was observed at a rate of 30.1%. Moderate-severe OSAS was detected in 64.4% of the patients. When the relationship between optimal inspiratory/ expiratory positive airway pressure (IPAP/EPAP) values determined by automatic bilevel positive airway pressure (ABPAP) titration and PFTs parameters were analyzed, a moderate negative correlation was observed between IPAP value and forced vital capacity (FVC) (L) (r=-0.432, p=0035)

Discussion: The results of this study show that PFTs parameters can be used to predict polysomnographic findings for patients with obstructive/ restrictive disorders. Almost two-thirds of the patients with obstructive sleep apnea (OSA)-related symptoms in this group were observed to have moderate-severe obstructive sleep apnea syndrome (OSAS). Based on our results in ROC analysis, we believe that it would be appropriate to recommend titration with bilevel devices, especially for patients with forced expiratory volume in one second (FEV1)<60% and maximum expiratory flow between 25% and 75% of FVC (MEF_{25-75})<30%. Bilevel devices may be useful for patients with reduced MEF_{25-75} (representing peripheral airways), through alveolar recruitment and pressure support.

Conclusion: In our study, we demonstrated that the optimal IPAP value for treatment had a positive correlation with the oxygen desaturation index (ODI) and AHI and a negative correlation with minimum finger pulse oximetry (SpO_2), as well as a negative correlation with FVC value. Simple spirometric data along with polysomnographic data can also be helpful when determining baseline pressures in bilevel positive airway pressure (BPAP) titration for OSAS patients with respiratory dysfunction.

Keywords: PFTs, FVC, AHI, OSAS, IPAP

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), which is characterized by a complete or partial obstruction of the upper airway during sleep, has a multifactorial etiology. It is known that craniofacial anomalies and obesity together with a decrease in lung volume play a role in its pathogenesis. The decrease in lung volumes causes a less caudal traction effect leading to the collapse in the pharyngeal airway (1,2). There are also studies showing that pharyngeal collapsibility decreases as a result of negative extrathoracic pressure and lung volumes exceeding functional residual capacity (3). Increases in respiratory system resistance, which can be measured with the forced oscillation technique (FOT), lead to an increase in OSAS severity, especially in obese patients. Changes in elastic recoil pressure, which is an important mechanical property of the lungs, are considered a liable pathway in the pathogenesis of OSAS, as the decrease in peripheral lung volumes (4,5). Regarding the relationship between easily accessible spirometric values and obstructive sleep apnea (OSA), there are conflicting results in studies conducted with different patient groups (6,7). In addition, pulmonary function

Corresponding Author: Deniz Çelik, drdenizcelik@hotmail.com
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test (PFTs) parameters can guide the choice of treatment in OSAS (8). Especially when OSAS is associated with respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease, the clinical results may deteriorate. For this group known as overlap syndrome, improvement in prognosis can be achieved and quality of life can increase with appropriate OSAS treatment (9). There is a common belief that conventional PFTs are not useful in the diagnosis of OSAS (10). However, this study aims to reveal the relationship between PFTs parameters and polysomnographic parameters. It aims to determine the guiding values in treatment selection, with the hypothesis that easily accessible PFTs parameters can be useful in clinical evaluation for patients with restrictive or obstructive type disorders.

MATERIAL AND METHOD

The ethics committee approval for this study was obtained by the University of Health sciences Keçiören Education and Training Hospital Clinical Studies Ethics Committee (Date: 14/09/2021, Decision No: 2012-KAEK-15/2367). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

One hundred and forty-six patients with obstructive and/or restrictive pulmonary dysfunction who underwent polysomnography in the sleep clinic of our hospital between June 2019 and December 2019 were included in the study. PFTs were performed at the time of admission to the sleep clinic. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, and maximum expiratory flow between 25% and 75% of FVC (MEF_{25-75}) values were obtained from PFTs reports in line with the standards of American Thoracic Society (ATS)/European Respiratory Society (ERS) (11). FEV1/FVC ratio below 0.70 was defined as an obstructive disorder. FVC below 80%, with a normal FEV1/FVC ratio, is defined as a restrictive disorder. Exclusion criteria included patients with a sleep time of <180 minutes in the polysomnography test and whose PFTs performance was not acceptable according to the ATS guideline (11).

The files of the sleep outpatient clinic and the results of polysomnography were reviewed retrospectively. Total sleep time, oxygen saturation by finger pulse oximetry (SpO_2), and apnea-hypopnea index (AHI) were obtained from the records of standard full-night polysomnography montages with four channels of the electroencephalogram, two channels of electrooculogram, one channel of chin electromyogram, the thermistor, airflow, inductive plethysmography for thoracoabdominal motion, electrocardiography and finger pulse oximetry (SpO_2). All records were scored according to the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2 (12).

Age, gender, body mass index (BMI), Epworth Sleepiness Scale (ESS) score, PFTs parameters, apnea-hypopnea index, nocturnal oxygen saturation, tolerable positive airway therapy modality, and pressures were recorded.

Nocturnal hypoxemia was defined as arterial oxygen saturation below 88% for at least 5 minutes during the all-night PSG test (13). Positive airway pressure (PAP) titration success was determined according to the criteria in the AASM guide (14).

Statistical Analysis

We used SPSS software version 21 for all analyses, and statistical significance was accepted as a p-value of <0.05. The variables were classified according to the normality tests including histograms, the ratio of the standard deviation to mean, and the The Kolmogorov–Smirnov test. The normally distributed variables were presented as mean± sd. The non-normally distributed variables were presented as median (25th-75th percentile). Nominal variables presented as number(%) were compared with a Chi-square test. Mann Whitney U test or Student-t test was performed to compare the distribution of two groups for numerical data. The receiving operator characteristic (ROC) curve analysis was used to determine a significant cut-off value for SpO_2, FEV1 and MEF_{25-75} in predicting the titration failure, nocturnal hypoxemia and need for oxgen support during the sleep. The sensitivity, specificity, positive and negative predictive values were also presented. The correlations between expired positive airway pressure (EPAP), inspired positive airway pressure (IPAP) and the clinical variables were calculated using the Spearman test.

RESULTS

Of 146 patients 34.9% were women and most (92.5%) had an obstructive disorder in PFTs. Of the patients with the obstructive disorder, 71 were being followed up with a diagnosis of COPD and 64 with a diagnosis of asthma. Interstitial lung disease was observed in 5 out of 11 cases (7.5%) with restrictive type disorder, and obesity resulted in restrictive disorder for the remaining 6 cases. Moderate-severe OSAS was detected in 64.4% of the patients. Simple snoring was observed in 5.5% of this population, all of whom were symptomatic in terms of sleep apnea whilst mild OSAS was observed at a rate of 30.1%.

Fourteen patients who were receiving long-term oxygen therapy at home were given 2 lt/min nasal oxygen during the PSG after recording at room air for at least 30 minutes was obtained. It was observed that for 12 of these patients

(85.7%), sleep-related hypoxemia persisted despite nasal oxygen support. For all patients with nocturnal hypoxemia, oxygen saturation in wakefulness (SpO_2 awake) was ≤ 92%. After the exclusion of 14 patients who were given oxygen support during PSG, the data of 51 patients with sleep-related hypoxemia were compared with 81 patients who were not hypoxemic.

It was observed that patients with nocturnal hypoxemia were older, and their BMI and AHI values were higher. All of the PFTs parameters, FVC%, FVC (L), FEV1%, FEV1 (L), FEV1/FVC, MEF_{25-75}%, were found to be statistically lower for these patients.

Also, the SpO_2 awake values of these patients were lower. ESS score and gender distribution were statistically similar between the groups (**Table 1**). Sleep-related hypoxemia was observed in 50.8% of the patients followed up with COPD and in 24.2% of the patients diagnosed with asthma. Sleep-related hypoxemia was observed in 27.6% of patients with positional OSAS (n=29) and 37% of patients with rapid eye movement (REM)-related OSAS (n=49).

Regarding the population, for which restrictive or obstructive disorders were found with pulmonary function tests, half of the patients did not attend or complete the titration tests. While titration was found to be successful for 16 of 21 patients who were titrated with automatic positive airway pressure (APAP) (76.2%); the titration test was successful for 23 (95.8%) of 24 patients who were titrated with automatic bilevel positive airway pressure (ABPAP). For ten patients, despite the optimal pressure support with bilevel positive airway pressure (BPAP) therapy, additional oxygen support to provide nocturnal oxygenation was required. It was observed that the group with failed APAP titration was similar to the successful group in terms of age, BMI, SpO_2 awake, and ESS score, but the PFTs parameters were significantly lower (**Table 2**). Similarly, it was observed that the group whose oxygenation improved only with ABPAP was similar to the group in need of additional oxygen in terms of age, BMI, wakefulness SpO_2 and ESS score, but all other PFTs parameters except the FEV1/FVC ratio were lower for the patients requiring additional oxygen (**Table 3**). With the ROC analysis, the optimal cut-off values were determined by selecting the 2 most ideal parameters according to the area under the curve (**Figure 1**).

FEV1 (L)<1.9 and SpO_2<90% for nocturnal hypoxemia; FEV1 (L)<1.5 and FEV1 %<50% for supplemental oxygen demand; FEV1 %<60% and MEF_{25-75} %<30% for APAP titration failure, were set as statistically significant cut-off values (**Figure 1-3**). Sensitivity, specificity, positive and negative predictive values of these limit values are shown in **Table 4**. In addition, when the relationship between optimal IPAP/EPAP (inspiratory/expiratory positive airway pressure) values determined by ABPAP titration and PFTs parameters was analyzed, a moderate negative correlation was observed between IPAP value and FVC (L) (r=-0.432, p=0035, **Table 5**).

Table 1. The comparisons of the characteristics between the patients with and without nocturnal hypoxemia

	Patients with nocturnal hypoxemia n=51 median (25^{th}-75^{th} percentile) n (%) mean±SD	Patients without nocturnal hypoxemia n=81 median (25^{th}-75^{th} percentile) n (%) mean±SD	p value
Gender (female, %)	21 (41.2%)	23 (28.4%)	0.129
Age	58.5±9.5	52.5±11	0.002
BMI (kg/m²)	34.3 (29.7-39.1)	31 (27.7-34.7)	0.003
ESS	7 (3-10)	8 (2.5-11)	0.963
AHI (events/hour)	29.6 (17.3-38.4)	16 (9.9-36)	0.005
ODI	20.2 (13.3-32.7)	12.3 (5.1-25.9)	0.001
Awake SpO_2	88 (86-89)	92 (91-94)	<0.001
Minimum SpO_2	69 (61-76)	83 (77-87.5)	<0.001
Mean SpO_2	87 (81-87)	91 (89-92.5)	<0.001
FVC (L)	2.2±0.76	3.1±0.84	<0.001
FVC (%)	64.1±17.2	79.7±17.7	<0.001
FEV1 (L)	1.5±0.56	2.2±0.64	<0.001
FEV1 (%)	51 (42-67)	72 (64.5-80)	<0.001
FEV1/FVC	69 (61-75)	73 (67-77)	0.013
MEF_{25-75} (%)	31 (21-50)	50 (40-59)	<0.001

BMI: Body mass index, ESS: Epworth Sleepiness Scale, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, SpO_2: Finger pulse oximetry, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, MEF_{25-75}: Maximum expiratory flow between 25% and 75% of FVC

Table 2. The demographic and polysomnographic differences of the patients with APAP titration failure

	Succesful titration with APAP n=16 median (25^{th}-75^{th} percentile) n(%) mean±SD	APAP titration failure n=5 median (25^{th}-75^{th} percentile) n(%) mean±SD	p value
Age	53.9±11.3	64.2±15.3	0.12
BMI (kg/m²)	31.2 (26.3-37.7)	29.7 (21.7-39)	0.680
ESS	9.5 (4.3-13)	9 (0-13.5)	0.648
AHI (events/hour)	29.9 (16.2-42.1)	42.6 (20.8-66.9)	0.28
ODI	19.7 (9.9-27.4)	31.8 (11.8-51.9)	0.19
Awake SpO_2	92 (91-94)	91 (87.5-92.5)	0.12
Minimum SpO_2	79 (68.5-89.8)	85 (59-91)	0.97
Mean SpO_2	91.5 (89.3-92.8)	70 (68-88.5)	0.006
FVC (L)	3.2±0.83	2.3±0.59	0.042
FVC (%)	85±17.1	64.23.3	0.015
FEV1 (L)	2.3±0.53	1.4±0.39	0.003
FEV1 (%)	78 (66-82.8)	51 (48-53.5)	0.001
FEV1/FVC	73 (71-76.8)	61 (58.5-65.5)	0.002
MEF_{25-75} (%)	50.5 (44.3-57)	24 (20-32.5)	0.001

BMI: Body mass index, ESS: Epworth Sleepiness Scale, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, SpO_2: Finger pulse oximetry, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, MEF_{25-75}: Maximum expiratory flow between 25% and 75% of FVC,

Table 3. The demographic and polysomnographic differences of the patients who need supplemental oxygen

	With supplemental oxygen n=10 median (25th-75th percentile) n (%) mean±SD	Without supplemental oxygen n=14 median (25th-75th percentile) n (%) mean±SD	p value
Age	60.9±8.4	56.4±9.4	0.244
BMI (kg/m²)	38.9 (34-46.1)	34.2 (30.8-39.1)	0.101
ESS	10 (0-16.5)	9.5 (2-12.3)	0.860
AHI (events/hour)	33.3 (20.4-49.2)	32.2 (15.8-55)	0.747
ODI	20.9 (12.8-52.5)	16.7 (14.5-36)	1.0
Awake SpO_2	87.5 (80.8-90)	89 (88-89.3)	0.191
Minimum SpO_2	61 (37.5-79)	73 (67.5-78.3)	0.135
Mean SpO_2	83.5 (72.5-87)	87.5 (86.8-89)	0.033
FVC (L)	1.7±0.64	2.7±0.97	0.007
FVC (%)	53.4±18.6	72.6±18.3	0.020
FEV1 (L)	1.1±0.43	1.9±0.70	0.004
FEV1 (%)	43 (31.8-52.8)	70 (47.3-76.5)	0.008
FEV1/FVC	66 (62.5-73)	73.5 (67-75.3)	0.142
MEF_{25-75} (%)	24 (15.5-32)	41 (30.3-51.1)	0.020

BMI: Body mass index, ESS: Epworth Sleepiness Scale, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, SpO_2: Finger pulse oximetry, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, MEF_{25-75}: Maximum expiratory flow between 25% and 75% of FVC

Table 4. The diagnostic value for the cut-offs determined for PFTs variables

	Sensitivity %	Specificity %	PPV %	NPV %
Cut-offs for APAP failure				
FEV1 <%60	100.0	93.8	83.3	100.0
MEF_{25-75}< %30	80.0	100.0	100.0	94.1
Cut-offs for nocturnal hypoxemia				
FEV1 (L)<1.9	84.3	69.1	63.2	87.5
SpO_2<%90	90.2	86.4	80.7	93.3
Cut-offs for Supplemental O_2				
FEV1 (L)<1.5	70.0	71.4	63.6	76.9
FEV1 <%50	70.0	71.4	63.6	76.9

APAP: Automatic positive airway pressure, SpO_2: Finger pulse oximetry, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, MEF_{25-75}: Maximum expiratory flow between 25% and 75% of FVC

Table 5. Correlations between iPAP/ePAP and clinical variables

	iPAP		ePAP	
	rho	p-value	rho	p-value
Age	0.093	0.67	0.051	0.81
BMI (kg/m²)	0.399	0.053	0.410	0.047
AHI (events/hour)	0.708	<0.001	0.546	0.006
ODI	0.553	0.005	0.410	0.047
Awake SpO_2	-0.303	0.150	-0.168	0.433
Minimum SpO_2	-0.453	0.026	-0.113	0.599
Mean SpO_2	-0.320	0.128	-0.463	0.023
FVC (L)	-0.432	0.035	-0.354	0.090
FVC (%)	-0.345	0.098	-0.268	0.206
FEV1 (L)	-0.396	0.056	-0.347	0.096
FEV1 (%)	-0.401	0.052	-0.292	0.166
FEV1/FVC	-0.109	0.613	0.011	0.958
MEF_{25-75} (%)	-0.231	0.278	-0.177	0.409

BMI: Body mass index, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, SpO_2: Finger pulse oximetry, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, MEF_{25-75}: Maximum expiratory flow between 25% and 75% of FVC

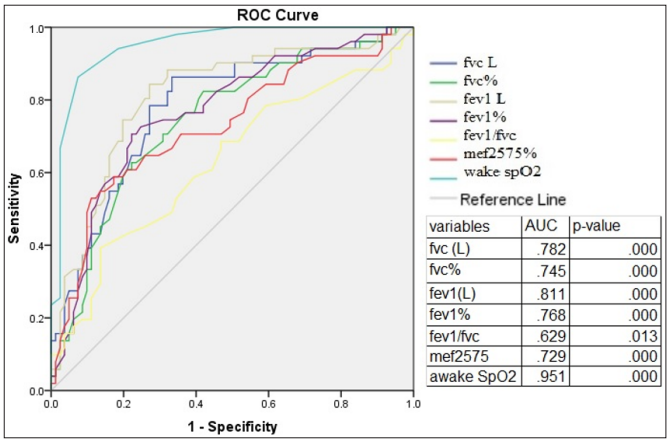

Figure 1. ROC curve analysis for nocturnal hypoxemia

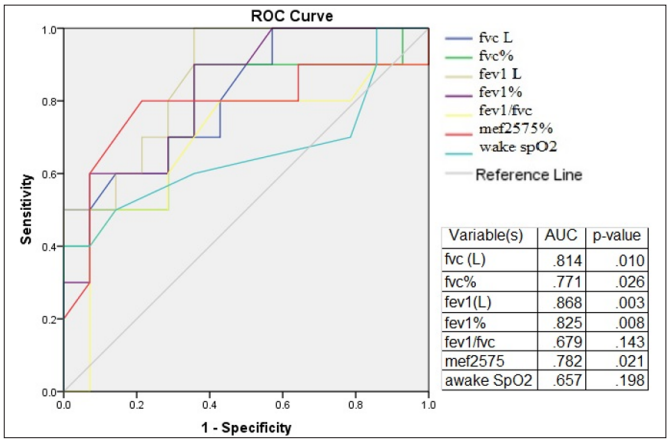

Figure 2. ROC curve analysis for APAP titration failure

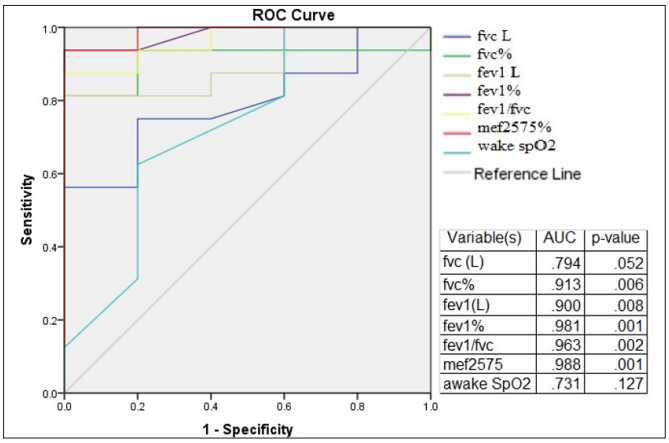

Figure 3. ROC curve analysis for oxygen therapy additional to BPAP

DISCUSSION

The results of this study show that PFTs parameters can be used to predict polysomnographic findings for patients with obstructive/restrictive disorders. Almost two-thirds of the patients with OSA-related symptoms in this group were observed to have moderate-severe OSAS. In the studies investigating the association of COPD-OSAS (overlap), the rate of OSAS detection in COPD patients was reported between 2.9% and

65.9% (15). The prevalence in our study is close to the upper limit of this wide range because all patients are symptomatic in terms of OSAS. For this population, nocturnal hypoxemia appears to be quite common in COPD patients and patients with REM-related OSAS. It has been revealed that for 70% of COPD patients and the majority of patients (85.7%) using long-term oxygen therapy (LTOT), nasal oxygen support alone is not sufficient to provide nocturnal oxygenation. It is known that especially obese OSAS patients' pulmonary functions are affected (1). On the other hand, Hoffstein et al. argue that there is no relationship between PFTs and OSAS for non-smoking OSAS patients without underlying lung disease (6). In this study, which mostly included patients with overlap syndrome, all of the PFT parameters (FVC%, FVC (L), FEV1 %, FEV1 (L), FEV1/FVC, MEF_{25-75} %) were statistically lower for the group with nocturnal hypoxemia. Especially, having an FEV1 value below 1.9 L and SpO_2awake<90% should be admonitory for nocturnal hypoxemia. It has been inferred that nocturnal desaturation in overlap syndrome correlates with daytime SpO_2 independent of BMI. For these patients, improvement in daytime SpO_2 is achieved with nocturnal CPAP therapy (16).

Abdeyrim et al. (10) pointed that for 263 OSAS patients without expiratory airflow restriction or lung disease, the increase in respiratory resistance and the decrease in functional residual capacity and respiratory conductance were associated with AHI independent of obesity. The decrease in functional residual capacity and increase in pharyngeal collapsibility is a known phenomenon that plays a role in the pathogenesis of OSAS (4,10). Our study reveals the importance of simple spirometric data for OSAS patients with lung disease. It has been proven that there is a statistically significant improvement in airflow restriction with CPAP treatment for patients with a basal FEV1 value below 79.1% (8). However, for this population with restrictive or obstructive disorders, the participation of the patients in the titration tests and the success of APAP titration are quite low (50%, 24%, respectively). On the other hand, ABPAP titration success was found to be quite high. Kuklisova et al. (17) inferred that CPAP titration was 23% unsuccessful in COPD-OSAS overlap syndrome and this was associated with nocturnal hypoxemia and daytime hypercapnia. In addition, they emphasized that FEV1 and FEV1/FVC values were lower for patients whose CPAP titration was not successful. Based on our results in ROC analysis, we believe that it would be appropriate to recommend titration with bilevel devices, especially for patients with FEV1<60% and MEF_{25-75}%<30%. Bilevel devices may be useful for patients with reduced MEF_{25-75} (representing peripheral airways), through alveolar recruitment and pressure support.

In addition to PAP devices, PFT values can be used to predict patients for whom oxygen therapy may be required. It has been inferred that deep nocturnal hypoxemia observed in the coexistence of COPD-OSAS, is associated with FEV1/FVC value (18). Oxygen therapy alone in nocturnal hypoxemia does not result in a proven benefit in some conditions, it may also lead to ventilation-perfusion mismatch by preventing hypoxic vasoconstriction (19). Our results show that when PFT results as FEV1 (L)<1.5 or FEV1%<50%, nocturnal oxygen therapy may be required in addition to PAP devices. Age, BMI, and AHI values were also higher for the group with nocturnal hypoxemia. It is remarkable that despite the statistical similarity in the other clinical parameters only PFT parameters were found to be statistically higher in patients with successful titration.

Titration tests are performed to determine the appropriate pressure or pressure range in PAP treatment. However, mathematical formulas have been proposed to provide a practical way to predict pressure values. Pressures calculated with these formulas are used to determine the initial pressure for treatment or titration. The variables used in these formulas recommended for CPAP are BMI, neck circumference, ESS score, polysomnographic data (such as AHI, RDI, ODI), gender, and the amount of smoking (20,21).

CONCLUSION

In this study, it was shown that the optimal IPAP value for treatment had a positive correlation with ODI and AHI and a negative correlation with minimum SpO_2, as well as a negative correlation with FVC value. Simple spirometric data along with polysomnographic data can also be helpful when determining baseline pressures in BPAP titration for OSAS patients with respiratory dysfunction.

This study contributes to the literature in terms of revealing the importance of PFTs parameters in a sleep clinic and guides the clinical use of these parameters. However, our study only examined cases with PFTs disorder. As mentioned above, the studies examining the relationship between PFTs results and polysomnographic data for people with normal PFTs parameters or the studies comparing these two groups would yield different results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee approval for this study was obtained by the University of Health sciences Keçiören Education and Training Hospital Clinical Studies Ethics Committee (Date: 14/09/2021, Decision No: 2012-KAEK-15/2367).

Informed Consent: All patients signed the free and informed consent form for the usage of their data.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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An evaluation of orthopaedic trauma patients presenting at the emergency department during lockdown in the COVID-19 pandemic

Hüseyin Sina Coşkun[1], Hikmet Çinka[1], İsmail Büyükceran[1], Göksel Gültekin Şahiner[2], Alparslan Yurtbay[2], Furkan Erdoğan[1], Ahmet Pişkin[1]

[1]Ondokuz Mayıs University, Faculty of Medicine, Department of Orthopedics and Traumatology, Samsun, Turkey
[2]Samsun Educatin and Research Hospital, Department of Orthopedics and Traumatology, Samsun, Turkey

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ABSTRACT

Aim: The SARS-CoV-2 virus causing COVID-19 disease, which started in Wuhan, China, in December 2019, rapidly affected the whole world and many precautions were taken in Turkey, as in other countries. The first case was recorded in Turkey on 11 March 2020, and the first COVID-19-related death on 15 March 2020. From that date, precautions were taken to prevent the spread of the disease, including the implementation of lockdowns and curfews. Although it was aimed to slow down public life during this period, orthopaedics and traumatology departments continued to function actively. The aim of this study was to evaluate orthopaedics and traumatology patients who presented at the Emergency Department (ED) during this period of lockdown.

Material and Method: The study included orthopaedic and traumatology patients who presented at the ED of Samsun Ondokuz Mayis University between 16 March and 1 June 2020, when there was a general lockdown. The data of these patients were retrospectively examined and were compared with the same period in 2019.

Results: During the specified period of the pandemic, 82 orthopaedics and traumatology patients presented at the ED, and in 2019, 109 patients presented. No statistically significant difference was found between the two groups in respect of age, gender, and the need for surgical procedure ($p > 0.05$). Although there was no statistically significant difference in age distribution, there was a decrease in the number of patients in the children age group during the pandemic period. No significant difference was found between the two groups in respect of the mechanism of injury, with the most frequent being a fall from a height of <1m and the least common was firearms injury.

Conclusion: Although there were small differences between the two periods examined in respect of the mechanism of injury of orthopaedic and traumatology patients, there was no significant difference. Therefore, in a pandemic period, treatment plans should be reviewed by taking appropriate precautions and establishing new algorithms.

Keywords: COVID-19, trauma, ethiology, lockdown

INTRODUCTION

The SARS-CoV-2 virus causing the novel coronavirus disease, COVID-19, within a short time rapidly spread, affecting the whole world (1,2). This outbreak was declared a global pandemic by the World Health Organization (WHO) in March 2020. Preventative measures were implemented to prevent the spread of diseases, such as moving education online, and sports and social activities were halted. Within the framework of these restrictions, lockdowns were implemented on some days in Turkey. However, as there remained a need for medical services even on the days when there was a lockdown, emergency medical services continued during this period. The orthopaedics and traumatology department is the leading department of those providing emergency services during this period. Trauma entails increased economic loss and morbidity for patients, and has become a major public health problem, which can be prevented (3,4). The WHO predicted that trauma would be the third leading cause of mortality worldwide in 2020 (5). Changes in the causes of bone

Corresponding Author: Hikmet Çinka, hkmtcnk@gmail.com
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fractures have emerged because of sociological changes in lifestyle during COVID-19 pandemic. Examining the epidemiology of fractures occurring as a result of trauma and taking precautions to prevent accidents causing fractures is known to be one of the most effective public health methods (6).

The hypothesis of this study was that there would be fewer patients presenting at the ED because of trauma during the lockdown period. The aim of the study was to determine the fracture characteristics of patients who presented at ED and were referred to the Orthopaedics and Traumatology Department of our centre during the lockdown period of the COVID-19 pandemic, and to thereby reduce the number of new fractures which may occur by increasing the precautions against the causes of fractures frequently seen during this period, and to show how the COVID-19 pandemic affected the orthopaedic and traumatology emergency procedures (7,8).

MATERIAL AND METHOD

The study was approved by Ondokuz Mayıs University Clinical Researchs Ethics Committee (Date: 23.07.2020, Decision Number: 506). In this retrospective study, all procedures and practices are in accordance with the ethical standards of the national/ institutional research committee and the 1964 Helsinki Declaration.

From the beginning of the COVID-19 pandemic, lockdowns were implemented at weekends in 31 provinces of Turkey, and were then gradually reduced within the plan for normalisation of life. The study included patients who presented at ED and needed orthpaedic consultation in the period of weekend curfews between 16 March 2020 and 1 June 2020. The data of these patients were retrospectively examined and then compared with data from the same period in 2019.

The data collected included demographic characteristics (age, gender), mechanism of injury, side and localisation of fracture, open or closed fracture, and fracture treatment model (conservative or surgery). The patients were separated into two groups as those who presented during the COVID-19 pandemic and those from the corresponding period in 2019. The mechanisms of injury were grouped as agricultural injury, traffic accident, fall at the same level (from <1m), fall from height (>1m), and others. Patients were excluded from the study if there was no fracture resulting from the trauma or if other systems were involved. The number of admissions was also evaluated by dividing the patients into 4 subgroups according to age: children (≤14 years old), young adults (15-44 years old), middle-aged adults (45-64 years old) and elderly patients (65 years and older).

Data obtained in the study were analyzed statistically using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM SPSS Corp., Armonk, NY, USA). The conformity of the in-group and inter-group variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Independent two-sample t-test was used to compare two independent groups with normal distribution, and Mann Whitney U test was used to compare two groups that were not normally distributed. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 82 orthopaedic and traumatology patients presented at our hospital during the specified period of the pandemic (16 March 2020- 1 June 2020 when lockdowns were implemented). This group comprised 50 (61%) males and 32 (39%) females. In the corresponding period in 2019, 109 patients presented, comprising 77 (70.6%) males and 32 (29.4%) females (**Table 1**). No significant difference was determined between the two groups of patients in respect of gender distribution (p=0.150).

Table 1. The epidemiological characteristics of the patients and the treatment applied to present at the Emergency Department for orthopedic injuries

	2019 n=109	2020 (Pandemic period) n=82	p value
Gender (Male/Female)	77/32 70.6%/29.4%	50/32 61%/39%	0.150
Age, (mean/median) (years), (min-max)	33.04/24.5 (4 months-92 years)	38.41/37.5 (1 day-86 years)	0.297
Treatment			0.169
Surgical treatment, n (%)	36 (33.1%)	34 (41.5%)	
Conservative treatment, n(%)	73 (66.9%)	48 (58.5%)	

The mean age of the patients was 38.41 years (range, 1 day-86 years) during the pandemic, and 33 years (range, 4 months-92 years) in 2019. No significant difference was determined between the two groups in respect of mean age (Table 1) (p=0.297). The patients were divided into 4 subgroups: children (≤14 years), young adults (15–44 years), middle-aged adults (45–64 years) and elderly patients (65 years and over). For both periods, patients in the children age group constituted the majority. But, the number of the patients in the children age group was determined to have reduced during the pandemic (**Figure 1**).

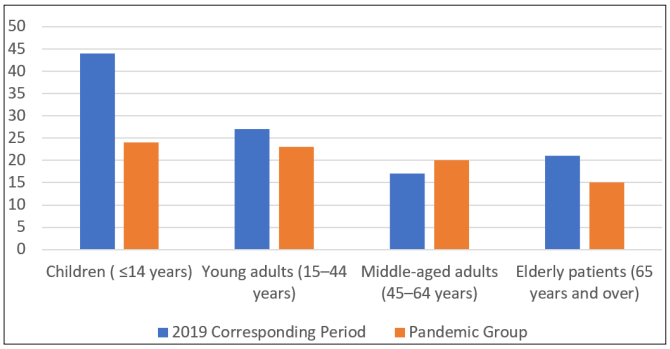

Figure 1. Age distributions of the patients

For the pandemic group, the proportion of fall from <1m height causing fractures was 53.6% (44/82), followed by minor trauma (11, 13.4%), traffic accident (8, 9.8%), fall from >1m height (7, 8.5%), soft tissue infection (6, 7.3%), agricultural injury (5, 6.2%) and firearms injury (1, 1.2%) (**Figure 2**).

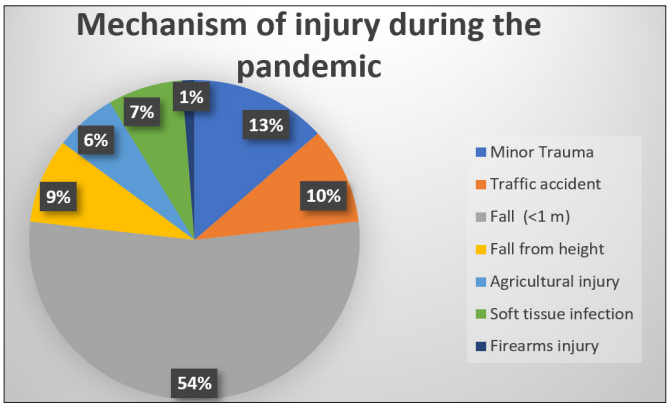

Figure 2. Distribution of patients according to the injury mechanism (Pandemic period)

For the patients presenting during the corresponding period in 2019, the proportion of fall from <1m height causing fractures was 48.6% (53/109), followed by minor trauma (18, 16.6%), traffic accident (14, 12.8%), fall from >1m height (7, 6.4%), agricultural injury (7, 6.4%), soft tissue infection (6, 5.6%) and firearms injury (4, 3.6%) (**Figure 3**).

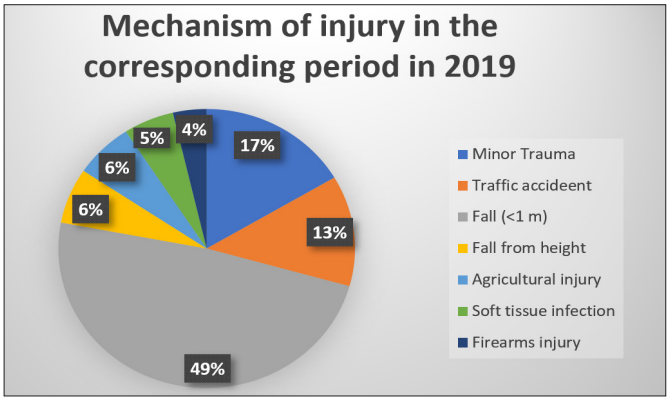

Figure 3. Distribution of patients according to the injury mechanism in 2019

Of the patients presenting during the pandemic, 48 (58.5%) could be followed up conservatively, and 34 (41.5%) had fractures that required surgery. Of the patients presenting in 2019, 73 (66.9%) were followed up conservatively, and 36 (33.1%) had a fracture pattern that required surgery. No statistically significant difference was found between the two groups in respect of the treatment methods (**Table 1**) (p=0.169).

DISCUSSION

Societal restrictions and lockdown during the coronavirus (COVID-19) pandemic have had a significant impact on the volume and nature of trauma admissions (9-11). Following the outbreak of COVID-19, precautions were taken in Turkey, just as throughout the world, to restrict the movement of people and reduce contact. The first case was recorded in Turkey on 11 March 2020, and then various restrictions were brought into force between 16 March and 1 June 2020 in the large cities throughout the country. One of the precautions was weekend lockdown. In this study, the effect of the lockdown was evaluated on the epidemiological characteristics of orthopaedic and traumatology patients who presented at ED.

The results of the study showed a decrease in the number of patients, but the differance was not statistically significant compared to the same period of the previous year. This decrease was thought to be due to patients being reluctant to go to the hospital for fear of contracting COVID-19 after a minor trauma.

When trauma centers around the world were examined during the pandemic, in Midland, New Zealand, there was seen to be a 43% reduction in patients presenting during a period of restrictions compared to pre-pandemic times. In that study, there was also observed to be a significant decrease in the Injury Severity Score values and a significant decrease in the numbers of traffic accidents and falls (12). Kamin et al. (10) examined ED cases in the lockdown period of February- April 2020, and found 80.5% decrease in motor vehicle accidents. In the current study, no significant difference was found between the two time periods in respect of motor vehicle accidents. A decrease in trauma cases associated with pandemics in the world has been previously reported. During the SARS pandemic in 2003, a trauma center in Taiwan reported a similar decrease in patients (13). In a single-centre, retrospective study conducted in Holland during the first COVID-19 lockdown (11 March-10 May 2020), which evaluated trauma patients presenting at ED, cases were observed to have decreased compared to 2019 and 2018 (14). In the same study, a significant decrease was found in sports injuries compared to the other periods. It was concluded that especially patients with minor trauma were reluctant to go to hospital because of concerns about the pandemic (14).

In the comparisons of the two groups in the current study, while there was no significant difference between the groups in respect of the mean age of the patients, when the age distribution was examined, there was seen to be a decrease in the children age group and an increase in the middle-aged adult group. The reason for the decrease in paediatric cases can be assumed to be that as a result of the lockdown, children were less active at home and less exposed to trauma. Similar results can be seen in literature (15-17). According to the results of a study by Susan et al. (18) in a level 1 trauma center, there was a significant decrease in the overall number of trauma-related admissions during the COVID-19 pandemic and especially during the lockdown period. Those results reflected a decrease in falls and traffic accidents. Another criteria investigated showed no significant increase in cases of self-harm and assaults. In the current study, the rate of self-harm injuries was not known.

The most common reason for presentation at ED in the current study was fall from the same level (<1m). Hip fractures as a result of falls within the home are often seen in the elderly population (19, 20). Hip fractures in the elderly patients, which are often observed in orthopaedics and traumatology practice, are treated with surgical methods. When these fractures occurring during the COVID-19 pandemic were compared with the control group, the rates were observed to be similar. The increased time spent in the home during the pandemic explains the similar rates of hip fractures resulting from a fall within the home. Bülent Güngörer found in his study that age is an independent risk factor in predicting the admission to intensive care unit of patients admitted to the emergency department with the diagnosis of COVID-19 (21). It should be kept in mind that preventive measures can be taken in the period of COVID-19 for this group, since it was determined in our study that there was no decrease in the number of elderly patients that presented at the emergency department.

A limitation of this study was the low number of patients. When it was assumed that there would only be emergency presentations at hospitals during the lockdown period, the study was designed using patients in a specific time interval. Despite this limitation, the study results provide information about the patient profile of those presenting at ED during the pandemic who were referred to the Orthopaedics and Traumatology Department.

CONCLUSION

The results of this study demonstrated that despite the lockdown restrictions implemented during the COVID-19 pandemic, there was no significant decrease in emergency trauma cases referred to orthopaedics and traumatology compared to the corresponding time period of the previous year. Although the injury patterns varied, as emergency trauma cases were seen at a high rate during the COVID-19 pandemic, treatment plans should be reviewed by establishing new trauma algorithms for this special period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ondokuz Mayıs Unversity Clinical Researchs Ethics Committee (Date: 23.07.2020, Decision Number: 506).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Original Article

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Gastroenterological disorders increase the prevalence of overactive bladder in females at various ages

Sedat Taştemur[1], Şenol Tonyalı[2], Buğra Bilge Keseroğlu[1], Mercan Taştemur[3], Mustafa Karaaslan[4], Bayram Yeşil[5], Mahmut Yüksel[5]

[1]University of Health Sciences, Ankara City Hospital, Department of Urology, Ankara, Turkey
[2]İstanbul University İstanbul School of Medicine, Department of Urology, İstanbul, Turkey
[3]University of Health Sciences, Ankara City Hospital, Department of Geriatrics, Ankara, Turkey
[4]Bingöl State Hospital, Department of Urology, Bingol, Turkey
[5]University of Health Sciences, Ankara City Hospital, Department of Gastroenterology, Ankara, Turkey

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ABSTRACT

Aim: In this study we aimed to determine the coexistence of overactive bladder in patients with gastroenterological disorders including hepatitis, cirrhosis and inflammatory bowel disease (IBD).

Material and Method: We prospectively collected the data of patients who admitted to the outpatient clinic of department of gastroenterology at Ankara Yüksek İhtisas Training and Research Hospital between May 2017 and February 2019. All patients with chronic gastroenterological disorders such as hepatitis and irritable bowel syndrome willing to participate after the verbal consent were included in the study

Results: A total of 289 female patients were included the study. The mean age of the patients was 49.9 ±13 years. The mean BMI value was 27.9± 4.5 kg/m². Among 289 patients, 135 (46.7%) had Hepatitis B, 53 (18.3%) had ulcerative colitis, 35 (12.1%) had Crohn's disease, 22 (7.6%) had autoimmune hepatitis, 19 (6.6%) had primer biliary cirrhosis, 13 (4.5%) had Hepatitis C and 12(4.2%) had celiac disease. The mean age of patients was similar between patients having OAB-v8 higher and lower than 8 (p=0.46). However, patients having OAB score>8 had higher BMI compared to patients who had OAB score <8, 29.1 ±5 vs. 27.2 ±4.1 kg/m², p=0.001. In multivariate regression analysis, BMI was the sole indicator of OAB (p=0.001) whereas age (p=0.46), menopause status (p=0.33), smoking status (p=0.97) were not.

Conclusion: The incidence of OAB in our patient cohort was higher than the reported incidence by that evaluating the patients with gastrointestinal disorders in terms of overactive bladder on routine follow-up might be suggested.

Keywords: Gastroenterological disorders, OAB-v8, overactive bladder

INTRODUCTION

Overactive bladder (OAB) is defined as urinary urgency with or without incontinence, usually accompanied with frequency and nocturia. OAB affects approximately 9-43% of the women population (1). However, a few people with OAB aspire for medical care for this disorder. OAB might lead to several health problems such as depression, sleep disorder and poor quality of life (2).

Ulcerative colitis and Chron's disease, known as IBD, constitute a major health burden and have detrimental effects on quality of life of affected patients. Since it is a chronic disease with unknown/ multifactorial etiology, several attempts and investigations have been held to control these inflammatory processes (3, 4). Currently accepted treatment choices include antibiotics, probiotics, folic acid antagonists, aminosalicylates, corticosteroids, thiopurines, methotrexate and anti-TNF agents (3, 5).

It has been estimated that approximately 2.5-3 million people are affected by IBD in Europe and there is still a tendency of increase in its incidence not only in Eastern Europe but also in Asia. The cumulative surgery rate was reported to vary between 37% and 61% 10 year after diagnosis and surgery rate was found to be declined in the last two decades (5). Inflammatory bowel disease is not only a bowel limited disease but also has several extra-intestinal signs and symptoms. Extraintestinal manifestations include Joint manifestations (arthropathies), cutaneous

Corresponding Author: Mustafa Karaaslan, mustafakaraaslan23@gmail.com
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manifestations (erythema nodosum, pyoderma gangrenosum), ocular manifestations which are found be frequent as high as 40% (5).

Furthermore, non-alcoholic fatty liver disease (NAFLD) was found to be associated with overactive bladder in women. The mechanism in this association was mainly based on NAFLD as being a component of metabolic syndrome. Thus, NAFLD might lead to atherosclerosis. However, mediators called hepatokines might also cause an inflammatory environment (6,7). There is currently not much study examining the relationship between hepatitis and overactive bladder.

To the best of our knowledge there is no study in the literature assesing the patients having IBD or liver diseases and bladder-related comorbidities in Turkish population. Thus, in this study we aimed the determine the coexistence of bladder disorders in patients that have gastroenterological disorders including hepatitis, cirrhosis and IBD.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ankara Yüksek İhtisas Training and Research Hospital Ethics Committee (Date: 28.12.2018, Decision No: 65). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We prospectively collected the data of patients who admitted to the outpatient clinic of department of gastroenterology at Ankara Yüksek İhtisas Training and Research Hospital between May 2017 and February 2019. All patients with chronic gastroenterological disorders such as hepatitis and irritable bowel syndrome willing to participate the study after the verbal consent were included the study. The inclusion criteria were as follow:

1. Both male and female patients older than age of 18
2. Having chronic gastroenterological disorders
3. Willing to participate the study and fulfill the questionnaire
4. Having regular follow-up.

The exclusion criteria included:

1. Being younger than 18 years of old.
2. Having a history of cancer
3. Receiving any chemo-radiotherapy for any reasons.
4. Being on medications like opioids or analgesics.
5. Having a pelvic organ prolapse
6. Having had surgery for cystocele or stress urinary incontinence
7. Having psychiatric disorders impairing or aggregating pain perception.

All patients were requested to fulfill the Overactive bladder V8 questionnaire which is a validated questionnaire in Turkish (8). The recorded parameters also included patient demographics, medical history and medications, complete blood count, urinalysis, serum urea and creatinine. The patients were divided into three groups according to symptom severity as in previous studies: Group 1- having OAB v8 score= 0-7, Group 2- having OAB v8 score=8-16, Group 3- having OAB-v8 >16 (9). Patients having OAB v8 score>7 assumed to have OAB.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY). Quantitative values are shown as mean ± SD (range) and qualitative values are shown as number and percentage. One-way ANOVA and the chi-squared test were used to compare dichotomous variables between groups. Student's t-test and the Mann-Whitney U-test were used to compare groups with normally and non-normally distributed continuous data, respectively. The level of statistical significance was set at $p< .05$.

RESULTS

A total of 289 female patients were included the study. The mean age of the patients was 49.9 ±13 years. The mean body mass index (BMI) was 27.9± 4.5 kg/m². Among 289 patients, 135 (46.7%) had Hepatitis B, 53 (18.3%) had ulcerative colitis, 35 (12.1%) had Crohn's disease, 22 (7.6%) had autoimmune hepatitis, 19 (6.6%) had primer biliary cirrhosis, 13 (4.5%) had Hepatitis C and 12 (4.2%) had celiac disease. 115 (39.8%) of the patients were in menopause. 31 (10.7%) were active smokers. Six patients (2.1%) had psychiatric disease including depression (n=3), anxiety (n=2) and panic attack (n=1). 78 patients (22.8%) had a OAB-v8 score higher than 8 (**Table 1**).

There was no statistically difference between patients having different gastroenterological pathologies in terms of OAB (p=0.34). The mean age of patients was similar between patients having OAB-v8 higher and lower than 8 (p=0.46). However, patients having OAB score>8 had higher BMI compared to patients who had OAB score <8, 29.1±5 vs. 27.2±4.1 kg/m², p=0.001. There was no difference between patients who had menopause and who had not in terms of OAB score, p=0.37. OAB frequency was similar between patients who were active smoker and who were not active smokers (p=0.11). In multivariate regression analysis, BMI was the sole indicator of OAB (p=0.001) whereas age (p=0.46), menopause status (p=0.33), smoking status (p=0.97) were not (**Table 1**).

Table 1. Comparison of patients according to OAB-v8 score

Variable	OAB-v8 score <8 (n=188)	OAB-v8 score>7 (n=101)	P value
Age (yr), mean±SD	49.5±12.5	50.7±13.5	.46
BMI (kg/m²)	27.2±4.1	29.1±5	.001
Crohn's disease	22 (62.9%)	13 (37.1%)	.62
Ulcerative colitis	35 (66%)	18 (34%)	
Autoimmune hepatitis	12 (54.5%)	10 (45.5%)	
Hepatitis B	94 (80.7%)	41 (19.3%)	
Primer biliary cirrhosis	12 (63.2%)	7 (36.8%)	
Hepatitis C	7 (53.8%)	6 (46.2%)	
Celiac disease	6 (50%)	6 (50%)	
On menopause			.37
Yes	71 (37.8%)	44 (43.6%)	
No	117 (62.2%)	52 (56.4%)	
Active smoker			.11
Yes	16 (8.5%)	15 (14.9%)	
No	172 (91.5%)	86 (85.1%)	
Hypertension			.80
Yes	14 (7.4%)	6 (5.9%)	
No	174 (92.6%)	95 (94.1%)	

BMI: Body Mass Index

DISCUSSION

OAB is defined as urgency with or without incontinence, often accompanied with frequency or nocturia. OAB may be idiopathic or related to neurologic disorders. The reported prevalence of OAB varies between 5.9 and 15.6% and strongly correlated with aging. OAB severity tends to increase in post-menopausal women which might be associated with decreased levels of estrogen (10). In our patient cohort, the prevalence of OAB was 22.8% which might indicate the high prevalence of OAB related to gastrointestinal disorders.

Etiology of OAB is considered multifactorial and ischemia related bladder dysfunction is one of the suggested mechanisms. It has been reported that atherosclerosis causes ischemia in bladder. Smoking is one of the leading factor of atherosclerosis. In previous studies, OAB symptoms have been shown to strongly correlated with aging and smoking (11).

Increased BMI was also reported to be associated with OAB symptoms(12). In this study, the mean age of the patients and smoking status of the patient who had OAB symptoms and who had not, were similar. This might be occurred due to the confounder effect of gastrointestinal disorders.

Cross organ sensitization has been widely studied and suggested in various conditions including trochal and abdominal organs. The organs reported to involve in cross organ sensitization phenomena including pelvic and lower abdominal organs: colon, rectum, urinary bladder, urethra, uterus and the prostate. It has been also suggested that urinary bladder is more vulnerable to cross-sensitization than other pelvic organs (13). In an former study in 1980's Whoewel et al. (14) reported that patient with irritable bowel syndrome may represent with symptoms related to urinary bladder such as nocturia, frequency, urgency and sense of incomplete bladder emptying. Gastrointestinal disorders generally classified under two groups as organic and functional. IBD consists of Crohn's disease and ulcerative colitis are organic digestive tract diseases characterized by chronic relapse and remittance of intestinal inflammation. The most frequent symptoms of IBD are abdominal pain, diarrhea, gastrointestinal bleeding as well as malnutrition (15). Although there have been several studies regarding to relationship between various gastroenterological disease and urological problems, there has not been a study examining overactive bladder in spectrum of gastroenterological diseases.

In a study by Haim et al. (16) the researchers found that 24.7% of the patients with Crohn's disease have urological symptoms which included cystitis, hydronephrosis, urolithiasis, enterovesical fistulas and retroperitoneal abscess. In a recent study by Xia et al. (17) authors investigate the mechanism of bladder hypersensitivity in patients with colonic inflammation. In their experimental study with rats, authors found that colon to bladder cross-sensitization exists with the upregulation of brain-derived neutrophic factor (BDNF) in dorsal the dorsal root ganglia.

Experimental animal studies have shown that chemically induced OAB might result in a hypersensitized colon and conversely induced colitis might alter bladder functions (18). There have been several studies evaluating the association between irritable bowel syndrome and overactive bladder (19,20). Matsumoto et al. (19) found that 33.3% of patients with OAB had concurrent IBS. And they concluded that assessing the defecation habits of patients is important when diagnosing or treating OAB. In contrast with Matsumoto et al., Kim et al. (20) reported no association between IBS and OAB. In our study, OAB was found to be present at 21.6% of our patient cohort which indicates the increased frequency of OAB compared to healthy population. These results might reflect the aforementioned mechanisms of cross-sensitization between abdominal organs. In concordance with the aforementioned studies, we found a high incidence of OAB in our patient cohort having gastrointestinal disorders. Although, the relationship between bowel diseases and OAB have been frequently studied, there is a lack of data assessing the possible relation between hepatic diseases and OAB. Almost all studies, reported a possible relationship based on the similar etiological risk factors for fatty liver and atherosclerosis.

Our study has limitations. The main limitation of the current study is that the heterogenous nature of the study population like some were in menopause and some were active smoker which might affect bladder habitus. Also, there was no so much patient in gastroenterological disease's subgroups that might cause statistical weakness.

CONCLUSION

We found a similar overactive bladder frequency in patients having various gastroenterological disease such as hepatitis, inflammatory bowel disease, celiac and autoimmune hepatitis. The incidence of OAB in our patient cohort was higher than the reported incidence by that evaluating the patients with gastrointestinal disorders in terms of overactive bladder on routine follow-up might be suggested.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara Yüksek İhtisas Training and Research Hospital Ethics Committee (Date: 28.12.2018, Decision No: 65).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

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Breast tuberculosis: analysis of 24 patients

Tibel Tuna[1], Serdar Coşkun[2]

[1]Ondokuz Mayıs University, Faculty of Medicine, Department of Chest Diseases, Samsun, Turkey
[2]Samsun Gazi State Hospital, Samsun, Turkey

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ABSTRACT

Introduction: Breast tuberculosis is a disease that is difficult to diagnose with its clinical appearance and can be confused with breast abscesses and breast carcinomas. In this study, we aimed to analyze 24 patients diagnosed with breast tuberculosis, followed up and treated.

Material and Method: Among 4489 patients examined in the breast diseases outpatient clinic between January 2012 and December 2020, patients diagnosed with breast tuberculosis were evaluated retrospectively. Demographic, clinical features, radiological findings, histopathological and microbiological findings of the patients were recorded. Diagnosis, treatment protocols and treatment outcomes were evaluated.

Results: A total of 24 breast tuberculosis cases were analyzed in the study. The mean age was 41.6 (28-64 years) and all patients were diagnosed for the first time. There was a history of oral contraceptive use in 10 patients. Among patients, 19 of them were in the reproductive age, and five patients were in the postmenopausal period. Four patients were in lactating period. On physical examination, breast mass was detected in 16 (67%) patients, abscess was present in 5 patients (20.8%), and sinus and discharge were evident in three patients (12.5%). Breast ultrasonography revealed a breast mass in 16 patients (67%), abscess in eight patients (33%), and axillary lymphadenopathy in six patients (25%). The diagnosis was made by core biopsy in 10 (41.6%) patients, fine-needle aspiration biopsy in three patients (12.5%), and incisional biopsy in 11 patients (45.8%). All patients were given quadruple antituberculosis therapy in the first 2 months for 9 months, and double antituberculosis therapy for 7 months. In addition to antituberculosis treatment, mass excision was performed in three patients (12.5%), segmental mastectomy in one patient (4.1%), simple mastectomy in one patient (4.1%), and abscess drainage were completed in eight patients (33.3%). Cure was achieved in all patients after treatment.

Conclusion: Breast tuberculosis is a rare disease that can be difficult to diagnose unless the disease itself is suspected. As the diagnosis of the disease is delayed, the disease becomes complicated and the need for surgical treatment increases as well as medical treatment. Although there are different opinions about the duration of the treatment, in our study, cure was achieved with 9 months of treatment and no recurrence was observed in the 1-year follow-up. Since 10 patients had a history of oral contraceptive use, further research is needed to understand whether oral contraceptive use is a predisposing factor in the development of breast tuberculosis.

Keywords: Extrapulmonary tuberculosis, diagnosis, management

INTRODUCTION

Tuberculosis is a global problem in the world and the second-leading infectious killer after COVID-19 in 2020. It is a disease that is associated with the death of 1.5 million people annually (1). Tuberculosis can infect many organs other than the lungs. Breast tuberculosis is a very rare form of extrapulmonary tuberculosis (2). Breast tuberculosis was first described by Sir Astley Cooper in 1829 (3). Breast tuberculosis is seen more commonly in developing countries, and since the main treatment of breast tuberculosis is antituberculous therapy, it is important to differentiate breast tuberculosis from other granulomatous diseases of the breast and breast cancer. The incidence of breast tuberculosis has been reported as 0.2%-6.8% (mean 1.7%), while in Western societies, it is reported as below 0.1% (2). This is explained by the fact that the breast tissue is resistant to M. tuberculosis (4).

Breast tuberculosis is generally classified as primary or secondary (5). It does not have a clinically apparent appearance. It can be confused with other breast diseases, breast abscesses and breast carcinomas. Since the most common manifestation is painful or painless

Corresponding Author: Tibel Tuna, tibeltuna@hotmail.com
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masses, it is difficult to diagnose breast tuberculosis with its clinical appearance. Other manifestations may include diffuse breast swelling, edema, nipple retraction, fistulization, multiple sinuses, skin ulcers, and recurrent abscesses (6-8).

Different diagnostic methods are available for breast tuberculosis, however, clinical suspicion is the first step in the diagnosis. Radiological tests (ultrasound examination, computed tomography, magnetic resonance and mammography) are not specific to achieve a diagnosis. Biological tests (culture, Ziehl-Neelsen staining) are of low sensitivity and time-consuming (2). Polymerase chain reaction (PCR) has high sensitivity, however, it has a higher cost and is not affordable for regions where tuberculosis is endemic (9). Fine needle aspiration biopsy is useful in making the differential diagnosis, but it is difficult to distinguish between granulomatous mastitis and sarcoidosis (10). Histopathological examination with biopsy of breast sections reveals granulomatous inflammation and caseification necrosis (7). The treatment of breast tuberculosis is carried out by applying medical therapy and accompanying surgery. Anti-tuberculosis treatment is usually given for 6 months or longer (11). In this study, we aimed to examine the demographic information, diagnosis and treatment methods of 24 patients who were diagnosed, followed up and treated in a chest diseases hospital in 9 years.

MATERIAL AND METHOD

The study was carried out with the permission of Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 25.03.2021, Decision No: 2021/146). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between January 2012 and December 2020, 24 patients with breast tuberculosis were evaluated retrospectively, out of 4489 patients examined in the breast diseases outpatient clinic. Demographic, clinical features, radiological findings, histopathological and microbiological findings of the patients were recorded. In the demographic evaluation of the patients, age, gender, educational status, and place of residence were recorded. Clinical features were evaluated as admission symptoms, location and appearance of the lesion, presence of axillary lymphadenopathy, lactation status, pre or postmenopausal status, use of oral contraceptives, and presence of concomitant disease. Breast ultrasound, mammography and chest X-ray were performed radiologically. Histopathologically, core needle biopsy, fine-needle aspiration biopsy, and incisional biopsy were performed and granulomatous inflammation including caseification necrosis was observed in patients. Microbiologically acid staining, Ziehl Nielsen staining and culture cultivation were performed and results were recorded. These patients who were diagnosed with breast tuberculosis received antituberculosis treatment for a total of 9 months, the first 2 months being quadruple with isoniazid (INH), rifampin (RIF), ethambutol (ETM), pyrazinamide (PZA),and the remaining 7 months with INH and RIF. The results of control appointment of the patients at the 12th month after diagnosis were evaluated. Data were computerized using SPSS v26.0 (Chicago, IL) and descriptive analyzes were presented as percentage and mean (minimum-maximum).

RESULTS

A total of 24 breast tuberculosis cases were examined. All of the patients were female. The mean age was 41.6 (28-64 years) and all patients were diagnosed with primary breast tuberculosis. Of the patients, nine (37.5%) lived in rural areas and 15 (62.5%) lived in the city center. Fourteen patients (58.3%) were from the working class and 10 of them (41.7%) were from the civil servant class. Seven patients (29.1%) had graduate education, and seventeen patients (70.8%) had undergraduate education. There was a history of oral contraceptive use in 10 patients (41.7%). While thirteen patients (54.1%) did not report any comorbidity, 11 patients (45.8%) had additional disease (5 patients had diabetes mellitus, two patients had hypertension, one patient had diabetes mellitus and hypertension, two patients had rheumatoid arthritis, one patient had ankylosing spondylitis). The sociodemographic characteristics of the patients were shown in **Table 1**.

Table 1. Sociodemographic characteristics

	(%)	N
Age	Mean 41.6 (min 28-maks 64)	24
Gender		
Female	100.0%	24
Male	0.0%	0
Marital status		
Married	83.3%	20
Single	16.7%	4
Profession		
Farmer	33.3%	8
Worker	12.5%	3
Housewife	12.5%	3
Officer	41.6%	10
Educational level		
Primary school	25.0%	6
Middle school	20.8%	5
High school	25.0%	6
University	29.1%	7
Region of origin		
Rural area	37.5%	9
City center	62.5%	15

Among patients, 19 (79.2%) were in the reproductive age, and five (20%) patients were in the postmenopausal period. Four (16.6) patients were currently lactating. Breast mass was detected in 16 (66.7%) patients, abscess in five (20.8%), and sinus and discharge in three (12.5%) patients. Lesions were located in the left breast in 11 (45.8%) patients, and in the right breast in 13 (54.2%) patients. The localization of the lesions in the breast was in the middle outer quadrant in nine cases (37.5%), in the upper outer quadrant in 12 cases (50%), and in the periareolar area in four cases (16.5%). Clinical features were shown in **Table 2**.

Breast ultrasonography was performed in all patients. A breast mass was detected in 16 (67%) patients, and abscess was detected in eight patients (33%). Axillary lymphadenopathy was negative in 18 patients (75%) and axillary lymphadenopathy was present in six patients (25%) on examination. Mammography was performed in nine patients (37.5%), and no specific finding was found. Biopsy, culture, and clinical response were evaluated to achieve a diagnosis. The core needle biopsy was performed in 10 patients (41.6%), fine needle aspiration biopsy in three patients (12.5%), and incisional biopsy in 11 patients (45.8%). Histological specimens showed epithelioid cell granulomas with caseous necrosis. While no growth was observed in the culture in 17 (70.8%) of the patients, the culture result was positive in seven patients (29.1%). The diagnostic methods and findings are summarized in **Table 3**.

After diagnosis, 11 patients (45.8%) were given antituberculosis treatment without any further procedure. In addition to antituberculosis treatment, mass excision was performed in three patients (12.5%), segmental mastectomy in one patient (4.1%), simple mastectomy in one patient (4.1%), and abscess drainage in eight patients (33.3%) (Table 4). All patients were given quadruple therapy (INH, RIF, PZA, ETB) in the first two months for nine months, and double therapy (INH, RIF) for seven months. Cure was achieved in all patients after treatment. Treatment applications were shown in **Table 4**.

DISCUSSION

In this study, we evaluated the diagnosis, follow-up and treatment results of patients with breast tuberculosis, which is a rare form of tuberculosis.

Tuberculosis is a common disease in endemic areas, however, solitary breast tuberculosis is rarely seen since the breast is more resistant to tuberculosis than other organs. Differentiation of granulomatous lesions (fungal, sarcoidosis, syphilis, plasma cell mastitis, actinomyces) encountered in the breast is necessary, and histopathological examination is required to

Table 2. Clinical characteristics

	(%)	N
Menopause		
Premenopausal	79.1%	19
Postmenopausal	20.9%	5
Location		
Right breast	54.1%	13
Left breast	45.8%	11
Location in breast		
Upper outer	50.0%	12
Middle outer	37.5%	9
Periareolar	16.6%	4
Risk factors		
Multiparity	50.0%	12
History of tuberculosis	4.1%	1
Lactation	16.6%	4
Presence of comorbidities		
Yes	45.9%	11
No	54.1%	13
Lactation		
Yes	16.6%	4
No	83.3%	20
Lung x-ray		
Normal	84.4%	21
Sequale	16.6%	3

Table 3. Diagnostic methods and results

	%	N
Diagnostic methods		
Fine needle aspiration biopsy	12.5%	3
Core needle biopsy	41.6%	10
Incisional biopsy	45.8%	11
Positive culture	29.1%	7
Clinical examination findings		
Mass	66.6%	16
Abscess	20.8%	5
Sinus	12.5%	3
Ultrasound findings		
Abscess	20.8%	5
Mass	66.6%	16
Axiller lymphadenopathy	25.0%	6

Table 4. Treatment methods

	%	N
Treatment		
Antituberculosis therapy	100.0%	24
Antituberculosis therapy + surgery	54.1%	13
Surgical treatment		
None	45.8%	11
Drainage	33.3%	8
Segmental mastectomy	4.1%	1
Simple mastectomy	4.1%	1
Excision	12.5%	3

distinguish it from malignant lesions. In this single-center retrospective study which analyzed the rare cases of breast tuberculosis demographically, clinically and therapeutically; it was observed that a diagnosis of breast tuberculosis can be achieved after initially suspecting from tuberculosis. It was also seen that the treatments given for at least 9 months were more effective and there was no recurrence observed in the annual follow-up.

Although breast tuberculosis can be seen in any age group, breast tuberculosis is rare in the elderly and individuals under the age of 18 (7,12,13) in the literature, while it is more common in women of reproductive age (14,15). In our study, 20.8% of the patients were in the postmenopausal period. The incidence of tuberculous mastitis increases in lactation, and 16.6% of our patients were in the lactation period. Enlargement and increase in vascularity in the breast canals during pregnancy and lactation cause infection (16). In particular, pregnancy predisposes to infection by suppressing the T-helper 1 pro-inflammatory response (17). Immunosuppressive use and HIV infection are among risk factors for primary and reactivation tuberculosis (18). None of the patients had HIV positivity. However, one patient was using TNF-alpha blocker with the diagnosis of Ankylosing spondylitis, and 1 patient was using steroids for rheumatoid arthritis. It was noteworthy that 10 of our patients (41.7%) had a history of oral contraceptive use. In a case-control study, Haleh et al. reported that multiparity, lactation duration, and the rate of use of oral contraceptives were significantly higher in patients with idiopathic granulomatosis mastitis compared to controls (19). In their retrospective study, Prasad et al. indicated that 54.79% of patients with idiopathic granulomatosis mastitis reported a history of oral contraceptive use without evidence of tuberculosis (20). This has raised doubts whether oral contraceptive use is a predisposing factor in the development of breast tuberculosis, however, further research is needed to demonstrate such an association.

In the process leading to the diagnosis of breast tuberculosis, the duration of the symptoms and the clinical course vary. While the time from symptom onset to diagnosis is a few weeks in western societies, this period is more than 7 months in eastern societies and Africa (8,21,22). It was observed that our patients presented within 4-6 weeks after the onset of symptoms, and were diagnosed within 8-10 weeks. It was thought that the socioeconomic status of the patients and the fact that they came from rural areas are factors in this delay. The most common symptom was a breast mass. Apart from this, abscesses and discharge were also seen. In our cases, 66% mass, 20.8% abscess and 12.6% sinus (discharge) were present. The diagnosis of breast tuberculosis was probably delayed due to the prescription of empirical antibiotic therapy as the first step in treatment for patients with abscess and discharge.

Although breast tuberculosis can be seen in both breasts simultaneously, it is very rare. The incidence rates in the right or left breast are not superior to each other (23-25). In our study, we did not detect simultaneous cases in both breasts, and there was no significant difference between the right and left breasts in terms of the presence of tuberculosis. In the literature review by Gianluca et al. (26), periareolar involvement was observed as 17.3%, similarly in our study, lesions were detected in the upper outer quadrant of the breast at a rate of 50%, in the middle outer quadrant of 37.5%, and in the periareolar region at a rate of 16.6%. In the same review, less than 10% of the patients were reported to have concomitant active pulmonary tuberculosis. In our study, there was no accompanying pulmonary tuberculosis, but 3 patients (16.6%) had previous tuberculosis sequelae.

The clinical appearance of the disease can be confused with many diseases. It is most often confused with fibroadenoma of the breast because the most common finding of fibroadenoma is a mass (27,28). It can also be confused with granulomatous and inflammatory diseases such as idiopathic granulomatous mastitis, sarcoidosis, wegener's granulomatosis, giant cell arteritis and other infectious diseases such as brucella, actinomyces, fungal infections and fat necrosis (27-29). Since there is no gold standard method for diagnosis, the diagnosis is made by demonstrating the microorganism and/or histopathologically. In some cases, the diagnosis is made by showing the response to antituberculosis treatment and pathology (31-33). While 71.9% of our patients were diagnosed with the pathological examination, microorganisms were only shown in 29.1% of the cases, similar to the low rate of diagnosis by showing microorganisms in the literature (6). The success rate of diagnosis by PCR has been reported as 50% (26), however, PCR diagnosis rates could not be evaluated in this study since this application was not performed in our cases

The most important diagnostic method for breast tuberculosis is histopathological examination. In the literature, the diagnosis rate was reported as 64% with fine-needle aspiration biopsy and 93% with biopsy (26), however, in our study, the rate of diagnosis was 12.5% with fine-needle aspiration biopsy, 41.6% with core needle aspiration biopsy and 45.8% with incisional biopsy. The reasons for the low diagnosis rate with fine-needle aspiration biopsy in this study were the presence of insufficient material and the lack of sufficient experience for cytological examination. The failed attempts with fine needle aspiration biopsy were completed with core needle or incisional biopsy.

There is no standard guideline for treatment. The mainstay of treatment consists of antituberculous therapy. While some physicians recommend 6 months of standard antituberculosis treatment, some authors recommend 9 months of antituberculosis treatment (2 months quadruple 7 months dual treatment). Although there are opinions that suggest 9-months of treatment has no extra contribution (34), there are publications reporting that the relapse rate was less with 9 months of treatment (33,35).

In our patients, recurrence was not observed in the 1-year follow-up of patients with 9 months of treatment. In breast tuberculosis, patients who usually require surgery are complicated cases that develop abscess and sinus formation and present to clinics late after the symptoms. Patients who underwent radical surgery have been reported as 4.6% in the literature (subtotal or total mastectomy) (8). The rate of radical surgery in our patients was 8.2% (segmental and simple mastectomy). Our patients who underwent radical surgery were diagnosed late and their breast tissue was destroyed. While minor surgical applications (abscess drainage, aspiration, sinus resection, necrotic tissue resection) were applied as 11.3% in the literature, it was applied to 33% of our patients. The reason for the higher rate of minor surgical procedures in our study compared to the literature is that they were performed for diagnostic purposes (26).

Limitations

Our study has some limitations. Firstly, the study was planned retrospectively. Since all patients were treated for 9 months, 9 vs 6-month treatment regimens were not compared. The patients' results at 12th month after 9 months of treatment were evaluated in this study. Longer follow-up could have provided clearer information in terms of follow-up results of recurrence. Since there was no cytologist in our hospital, fine needle aspiration biopsy could not be fully utilized for diagnostic purposes.

CONCLUSION

In conclusion, breast tuberculosis is still a rare disease that can be difficult to diagnose unless the disease itself is suspected, despite the increasing diagnostic and therapeutic possibilities. The most important point in diagnosis is to suspect the disease first. As the diagnosis of the disease is delayed, the disease becomes complicated and the need for surgical treatment increases as well as medical treatment. Thus, as the diagnosis is delayed, it becomes more difficult to protect the breast, and psychological and social effects increase after breast surgery in women of reproductive age. It was noteworthy that 10 patients (41.7%) had a history of oral contraceptive use, however, whether oral contraceptive use is a predisposing factor in the development of breast tuberculosis needs further investigations. Although there are different opinions on the duration of the treatment, no recurrence was observed in 9 months of treatment at 1-year follow-up. Therefore, we suggest that 9 months of treatment is ideal to prevent recurrence.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 25.03.2021, Decision No: 2021/146).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Sepsis induced coagulopathy score and D-dimer levels in COVID-19 patients followed in intensive care; what has changed in COVID era?

Ayşe Ayyıldız[1], Nurdan Çobaner[2], Birgül Yelken[1]

[1]Osmangazi University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskişehir, Turkey
[2]Van Training and Research Hospital, Intensive Care Clinic, Van, Turkey

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ABSTRACT

Aim: This study was planned to compare the extent of hypercoagulopathic complications in COVID-19 pneumonia with that of last year's pneumonia cases which consist of by other agents.

Material and Method: The data of patients with pneumosepsis due to non-COVID-19 causes between 01 April-30 June 2019 and COVID-19 pneumosepsis patients between 01 April-30 June 2020,were analyzed retrospectively. Demographic data, comorbidities, SOFA scores, SIC scores, D-dimer levels, coagulopathic complications, mortality and discharge status of patients diagnosed with pneumosepsis and treated in both periods were recorded

Results: While sequential D-dimer measurements did not show a significant change in the 2019 group, it was observed that it increased significantly in the 2020 group ($p<0.05$). When we analyse the coagulopathic complications,we saw that submassive pulmonary embolism was recorded in one patient in the 2019 group.In the 2020 group, one patient had disseminated intravascular coagulation (DIC) and one patient had massive pulmonary embolism.

Conclusion: In our study, we did not find a significant difference in SIC scores and mortality rates between pneumosepsis patients in last years and COVID-19 pneumosepsis patients.

Keywords: COVID-19, coagulopathy, sepsis

INTRODUCTION

SARS-CoV-2 is a member of the beta coronavirus family and is the third coronavirus identified in the pandemic type (1). The potential for multiple organ damage is quite high, and these patients should be evaluated as multisystemic (2). With current literature, it has been observed that coagulopathic complications can frequently occur in COVID-19 infection. The mechanisms of these coagulopathic complications are not yet understood and many hypotheses have been proposed (3).

Similar to SARS-CoV, SARS-CoV-2 can enter host cells and directly damage endothelial cells via the angiotensin converting enzyme-2 (ACE-2) receptor. The existing comorbidities of the patients, immobility, venous stasis and high inflammation secondary to sepsis can be listed as other causes of coagulopathy. Activation of host defense systems (activation of humoral and cellular immunity) in sepsis gives rise to the concept called thromboinflammation or immunothrombosis (4). During the activation of humoral and cellular immunity pathways, increased inflammatory mediators cause platelet aggregation , peripheral vasoconstriction resulting from increased thromboxane production and endothelial dysfunction. Thrombin, which is formed by these mechanisms, increases the risk of coagulation (5).

COVID-19 coagulopathy can occur in different coagulopathic forms such as sepsis induced coagulopathy (SIC), thrombotic microangiopathy, disseminated intravascular coagulation (DIC), antiphospholipid syndrome, hemophocytic syndrome (6). Shock and development of DIC are two important causes of multiple organ damage in sepsis patients. DIC development in patients is an important predictor of mortality. Since early diagnosis is vital, it should be followed closely (7,8). Sepsis-induced coagulopathy scoring is a scoring system

Corresponding Author: Ayşe Ayyıldız, drayseayyildiz@gmail.com
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created by adding platelet count and INR values to the Sequential Organ Failure Assessment (SOFA) scoring data. It is the first scoring system specially designed for coagulation disorders in sepsis after sepsis-3 definitions. In the early diagnosis and treatment of coagulopathic pathologies, regular follow-up of these scoring systems is recommended to reduce mortality (9).

This study was planned to compare the extent of these hypercoagulopathic complications in COVID-19 pneumosepsis worldwide with the scores of pneumosepsis cases that occurred with other pneumosepsis agents last year.

MATERIAL AND METHOD

The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Researchs Ethics Committee (Date: 16.10.2020, Decision No: 14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In our study, the data of pneumosepsis patients with different etiological agent between 01 April-30 June 2019 and the data of COVID-19 pneumosepsis patients between 01 April-30 June 2020 were analyzed retrospectively. In the 2019 group, the number of patients followed in the intensive care unit was 92, and 24 patients had a diagnosis of pneumosepsis. In the 2020 group, the number of patients followed in the intensive care unit was 145, and 57 patients were diagnosed with pneumosepsis. The number of patients with positive COVID-19 PCR test results is thirty-two. Patients with a previous history of deep venous thrombosis in both groups were excluded from the study. SOFA score and SIC score were calculated every other day for the patients during their stay in the intensive care unit. D-dimer levels were followed consequtive as well as SOFA and SIC scoring. Values above 0.5 mg/L were accepted as the upper limit. Four patients in 2019 group and 2 patients in 2020 group were excluded from the study because they did not have a 3 consecutively calculated SIC score. Fifty patients' data were analyzed. Thrombosis prophylaxis was applied to all patients according to the recommendations of the International Society for Thrombosis and Hemostasis (ISTH). Low molecular weight heparins (LMWH) are routinely used for prophylaxis. Heparin therapy was initiated in patients with low renal clearance. When a thromboembolic complication developed, the dose of LMWH was increased by 25% and the treatment dose was increased. Demographic data, comorbidities, SOFA scores, SIC scores, D-dimer levels, coagulopathic complications, mortality and discharge status of patients diagnosed with pneumosepsis and treated in both periods were recorded.

Statistical Analysis

The analysis of the data was made with the SPSS-25 program and it was worked with a 95% confidence level. Frequency (n) and percentage (%) for categorical variables; Mean (X) and standard deviation (sd) statistics are given for numerical (quantitative) variables. In the comparison of the measurements according to the group, independent groups were used with t/Mann Whitney tests; Comparisons with respect to time were analyzed by repeated ANOVA/Friedman tests, and the relationship between the group and the variables was analyzed using the Chi-square test. p value <0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference between the groups in terms of gender and age average (p>0.05) (**Table 1**). There was also no significant difference between the groups in APACHE II scores and comorbidities (p>0.05) (**Figure 1**). The mean age was 72.16±13.28 years and the mean APACHE-II score was 18.27±8.82.

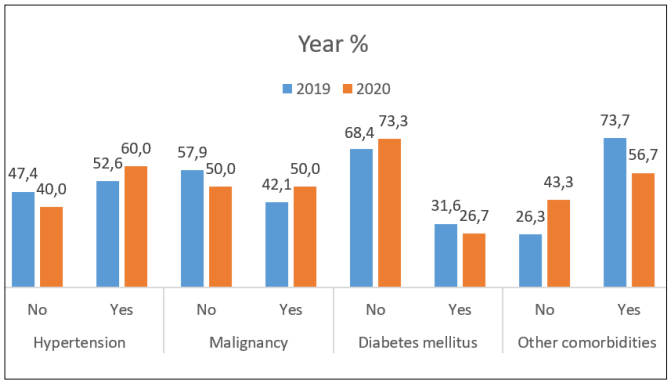

Figure 1. Comorbidities of patients

Table 1. The relationship of groups with gender, age and APACHE II

	Year		Total	p
	2019	2020		
Gender				
Male	8 (42.1)	16 (53.3)	24 (49)	0.636
Female	11 (57.9)	14 (46.7)	25 (51)	
Age	69.37±15.39	73.93±11.69	72.16±13.28	0.245
APACHE II	18.42±9.51	18.17±8.52	18.27±8.82	0.923

Although there was no statistically significant difference between the groups in terms of SOFA score averages, consecutive measurements of SOFA scores were statistically significant. (p<0.05). Consecutive measurements increased over time in both groups.This increase of consecutive SOFA scores over time did not show a statistically significant difference between the groups. (p>0.05) (**Figure 2**).

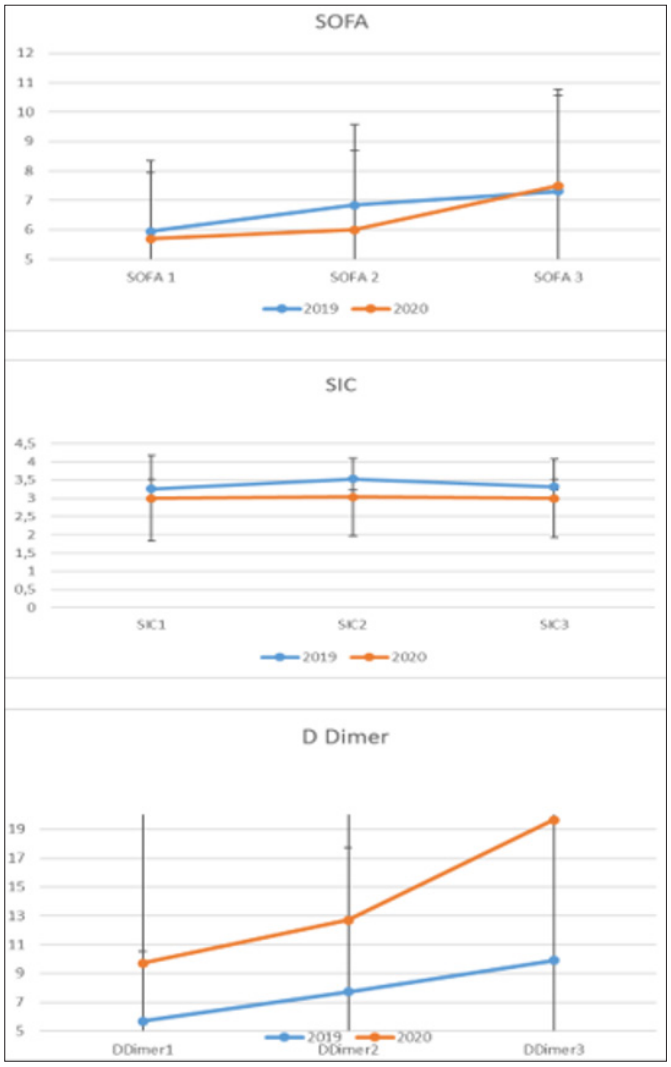

Figure 2. Levels of D-dimer, SOFA and SIC scores by groups

There was no statistically significant difference between the groups in terms of SIC scores (p>0.05). Consecutive measurements of SIC scores also did not show a statistically significant difference in both groups. (p>0.05). The change of SIC scores over time also did not show a statistically significant difference between the groups. (p>0.05) (**Table 2**).

Table 2. Change of SOFA and SIC measurements over time and the effect of groups

	Year		Total	p
	2019	2020		
SOFA 1	5.95±2.01	5.7±2.67	5.8±2.42	0.731
SOFA 2	6.84±2.73	6±2.7	6.33±2.72	0.296
SOFA 3	7.32±3.25	7.5±3.28	7.43±3.23	0.848
SOFA*Time				0.000*
SOFA*Year				0.304
SIC 1	3.26±1.1	3±1.17	3.1±1.14	0.437
SIC 2	3.53±1.17	3.03±1.07	3.22±1.12	0.136
SIC 3	3.32±1.29	3±1.08	3.12±1.17	0.361
SIC*Time				0.463
SIC*Year				0.628

There was no statistically significant difference between the groups in terms of the mean D-dimer levels (p>0.05). However, consecutive measurements of D-dimer levels show a statistically significant difference (p<0.05). Consecutive measurements have increased over time in both groups. Consecutive D-dimer measurements did not change significantly over time in the 2019 group (p>0.05), while it increased significantly in the 2020 group. (p<0.05) There was no statistically significant relationship between the d-dimer level and mortality between the groups. (p>0.05) (**Table 3**).

Table 3. Analysis of consecutive measurements of D-dimer levels between groups and their relationship with mortality rate

	Year		Total	p
	2019	2020		
D-dimer 1	5.7±4.79	9.72±10.88	8.13±9.12	0.137
D-dimer 2	7.71±10.03	12.71±15.2	10.77±13.54	0.124
D-dimer 3	9.91±13.91	19.65±20.75	15.87±18.86	0.078
D-dimer*Time				0.002
D-dimer*2019				0.268
D-dimer*2020				0.006
Result				0.418
Ex	11 (57.9)	22 (73.3)	33 (67.3)	
Discharge	8 (42.1)	8 (26.7)	16 (32.7)	

Analyzing the coagulopathic complications, submassive pulmonary embolism was recorded in one patient in the 2019 group. In the 2020 group, one patient had DIC and one patient had massive pulmonary embolism.

DISCUSSION

When the patients were analyzed in this study, it was seen that two homogeneous groups were formed similar in terms of age, gender, comorbidity and APACHE scores, and each significant result was very important in terms of showing us the specific differences in COVID-19 pneumonia. When we look at the results, we could not find a significant difference in terms of coagulopathic parameters in the pneumonia groups of the last two years. We are of the opinion that there is no increased coagulopathic process specific to COVID-19 pneumonia.

Autopsy series performed in the early stages of the pandemic had great repercussions all over the world, and the opinion that COVID-19 has high coagulopathic effects has been accepted. In a study by Carsana et al. (10) most of the patients were found to have fibrin thrombus (33/38). D-dimer levels were high in all cases. Likewise, the appearance of capillary microthrombus and pulmonary embolism in the autopsy series conducted by Menter et al. (11) proved once again how important coagulopathy is in the pathogenesis of COVID-19 infection.

Wichmann et al. (12) reported that there was an unpredictably high level of deep vein thrombosis among the COVID-19 patients who died in their study, and they directly observed massive pulmonary embolism in 33.3% of the cases. They hypothesized that the main determinant of mortality is coagulopathic complications. In our study, massive pulmonary embolism was developed in one patient in the 2020 group and resulted in mortality. Patients diagnosed with pneumosepsis with similar comorbidities and similar APACHE scores were compared; There was no significant difference in the mortality rate of the patients in the 2020 group compared to the 2019 group.

In a study conducted by Zhou et al. (13) D-dimer levels were found to be significantly higher in patients with mortality in Covid 19 pneumonia, and it was emphasized that it was an independent indicator of in-hospital mortality. It has been hypothesized that the major role in the increase of D-dimer may be due to the increased systemic pro-inflammatory activation triggering the prothrombotic process (14). In a retrospective study by Wang et al. (15) D-dimer levels of 138 patients were shown to be significantly different between patients who required ICU and those who did not (414 mg/L vs. 166 mg/L). They hypothesized that the significant increase in D-dimer was associated with the formation of a large number of microthrombus in the body.

In our study, consecutive measurements of D-dimer levels show a statistically significant difference. Successive measurements have increased over time but there was no statistically significant relationship between the d-dimer level and mortality between the groups.

After studies showing that the addition of anticoagulant therapy to treatment protocols reduces mortality, anticoagulant treatment protocols were routinely applied to each patient, as long as there were no contraindications in our country as in the world. Coagulopathy scores were followed at least every other day in line with the recommendations (6,16,17).

Although the International Thrombosis and Hemostasis Association (ISTH) recommends follow-up with DIC criteria for the diagnosis of DIC, they also stated that these criteria are not suitable for early diagnosis. For this reason, ISTH proposed a new scoring system called "sepsis induced coagulopathy"which is the first scoring system specifically design for coagulation disorders to facilitate early diagnosis and rapid interventions of DIC, and this scoring system has taken its place in the new sepsis 3 definitions (18,19). Sepsis coagulopathy can progress to fatal DIC. Diagnosing DIC makes sepsis management easier and is associated with better outcomes (20). In our study, patients were followed every other day using the SIC score.

Our study has limitations such as the limited number of patients in the groups and its retrospective nature. however, we believe that it will be a pioneer for large-scale studies to be carried out in the future.

CONCLUSION

As a result of the parameters we examined between these two homogeneously formed groups with no significant difference between age and comorbidities, we concluded that the coagulopathic effect of covid pneumonia was not different compared to pneumonias in other years.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Researchs Ethics Committee (Date: 16.10.2020, Decision No: 14).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

HEALTH SCIENCES
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Are YouTube videos a sufficient resource for informing patients in the treatment of rotator cuff tears?

Levent Umur[1], Serkan Sürücü[2]

[1]Acıbadem Kadıköy Hospital, Department of Orthopaedics and Traumatology, İstanbul, Turkey
[2]University of Missouri Kansas City, Department of Orthopaedics and Traumatology, United States of America

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ABSTRACT

Background: The aim of this study was to evaluate the information quality of YouTube videos on rotator cuff tear treatment.

Material and Method: A YouTube search was performed using the keyword 'rotator cuff tear' to determine the first 100 most watched videos related to rotator cuff tears. A total of 57 videos met our inclusion criteria and were included in the study. Videos were evaluated for information quality by using DISCERN, the Journal of the American Medical Association (JAMA), and rotator cuff informational assessment (RCIA) scores. Number of views, time since upload, view rate, number of likes, number of dislikes used to calculate the video power index (VPI) and these criteria were used to determine video popularity. Video length (sec), video source and video content were also evaluated and used for correlation evaluations.

Results: The mean DISCERN score was 33.81 (21-56), the mean JAMA score was 3.05 (1-4), and the mean RCIA score was 3.63 (0.5-7.5). Statistical analysis revealed that, independent of the video source and popularity, the videos were informationally poor and inadequate. The only significant correlation was between video length and data source.

Conclusion: This present study demonstrated that the quality of information provided by YouTube videos about rotator cuff tear treatment was poor. The generation of survey systems for informational videos and the provision of accurate and thorough informational videos by professional health organizations will be the best ways to inform patients.

Keywords: Rotator cuff tear, YouTube, video information quality, patient education

INTRODUCTION

Patients above the age of 60 are more likely to suffer from rotator cuff injuries (1). Its incidence gradually increases with the increasing age of patients (2). In individuals over the age of 80, the rotator cuff tear incidence is more than 50% (3). Rotator cuff tears can be asymptomatic, and in some patients, they may also cause symptoms such as severe limitation of motion and pain (4). While conservative treatment is sufficient in asymptomatic patients, surgical treatment is required in symptomatic patients (5).

On the internet, there are several videos designed to inform people about rotator cuff repair. YouTube is one of the platforms where the most videos are uploaded and viewed on the internet (6). Many doctors and healthcare organizations share informational videos and almost all patients seeks for online videos as a second opinion. But this tendency raised a concern about the quality and accuracy of the medical informational videos hosted by YouTube is not a peer-reviewed platform (7). For this reason, the number of likes and views of the videos can create a quality video perception of the patients and cause false information (8). In addition, videos prepared for commercial purposes with commercial concerns may have negative consequences for the treatment of patients (9).

The purpose of this study was to assess the quality of YouTube videos on the diagnosis and treatment of "Rotator Cuff Tears." The evaluation was done from the perspective of a patient seeking medical information.

MATERIAL AND METHOD

This study was conducted as a YouTube research, there is no need for ethics committee approval.

Videos available on YouTube on 3 November 2020 were scanned using the keyword "Rotator Cuff Tear". The first 100 videos we encountered after the search were evaluated. Non-English, advertising content, less than 1 minute and longer than 20 minutes were excluded from the study.

Corresponding Author: Levent Umur, dr.flumur@gmail.com
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The first fifty-seven most watched videos meeting the appropriate criteria were included in our study.

The total number of visits, comments, likes, dislikes and the time interval after upload were recorded. Additionally, video popularity was determined using the video strength index (VPI) values [(likes/dislikes) *100]. We also recorded the video's duration (seconds), provider, and contents.

Two different orthopedic physicians analyzed the videos twice at different times using the DISCERN, Journal of the American Medical Association (JAMA), and Rotator Cuff Informational Assessment (RCIA) scoring systems.

The DISCERN scoring system is composed of 3 sections and has a total of 16 questions. These three sections include 8 questions concerning information's reliability, 7 questions about treatment information, and a question about the overall quality of information (**Table 1**).

The JAMA scoring system assigns 1 point to each of four criteria (Authorship, Attribution, Disclosure, and Currency), for a total of 4 points. According to the JAMA scoring system, the least valuable information is valued 1 point and the most valuable information is valued 4 points (**Table 2**).

RCIA is a novel scoring system that consists of 7 sections (definition and pathoanatomy, risk factors and associated conditions, signs and symptoms, imaging, nonoperative treatment, operative treatment and complications), and the overall RCIA score ranges between 0 and 10 (**Table 3**).

The relationships between VPI and DISCERN, JAMA, and RCIA scores, VPI and video source, video duration and DISCERN, JAMA, and RCIA scores, and view rates and DISCERN, JAMA, and RCIA scores were studied. To avoid misinterpretation related to the age of the videos, the view rate (total number of views divided by time since upload) was used for statistical analysis rather than the total number of views.

Variables were defined using descriptive data (mean, standard deviation, standard error, minimum, median, and maximum for data that showed normal distribution, and median, minimum, maximum, and IQR for data that did not show normal distribution). Pearson's correlation coefficient was calculated to evaluate the relation between normally distributed continuous variables. Due to the non-normal distribution of the parameters, the Kruskal-Wallis test was used to compare groups and the Mann-Whitney U test (with Bonferroni's correction) to identify the group that caused the difference. Intergroup differences were compared using the one-way ANOVA test. IBM SPSS Statistics 22.0 was used to conduct the statistical analysis. The statistical significance level was set at 0.05.

Table 1. DISCERN scoring system

		No		Partially		Yes
		1	2	3	4	5
	Section-1: Is the publication reliable?					
1	Are the aims clear?					
2	Does it achieve its aims?					
3	Is it relevant?					
4	Is it clear what sources of information were used to compile the publication (other than the author or producer)?					
5	Is it clear when the information used or reported in the publication was produced?					
6	Is it balanced and unbiased?					
7	Does it provide details of additional sources of support and information?					
8	Does it refer to areas of uncertainty?					
	Section-2: How good is the quality of information on treatment choices?					
9	Does it describe how each treatment works?					
10	Does it describe the benefits of each treatment?					
11	Does it describe the risks of each treatment?					
12	Does it describe what would happen if no treatment is used?					
13	Does it describe how the treatment choices affect overall quality of life?					
14	Is it clear that there may be more than one possible treatment choice?					
15	Does it provide support for shared decision-making?					
	Section-3: Overall rating of the publication?					
16	Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices.					

Table 2. JAMA quality assessment

Authorship	Authors and contributors, their affiliations, and relevant credentials should be provided
Attribution	References and sources for all content should be listed clearly, and all relevant copyright information should be noted
Disclosure	Website "ownership" should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest
Currency	Dates when content was posted and updated should be indicated

Table 3. RCIA scoring system				
Rotator Cuff Informational Assessment				
No	**Criteria**	**Sub-criteria**	**Score**	**Total Score**
1	Definition & Pathoanatomy (Max 2 pts)	Cause (Degenerative/Trauma) (1 pt) Tear Morphology (Full-Partial) (1 pt) Rotator Cuff Function (0.5 pt)		
2	Risk Factor & Associated Conditions (Max 1 pt)	Age (0.5 pt) Biceps Tendon Pathology (0.5 pt) Subacromial Impingement (0.5 pt) Calcific Tendonitis (0.5 pt)		
3	Signs & Symptoms (Max 1 pt)	Pain (Overhead-Night) (0.5 pt) Loss of Active ROM (0.5 pt)		
4	Imaging (Max 1 pt)	MRI (1 pt) X-Ray (0.5 pt)		
5	Non-Operative Treatment (Max 1 pt)	PTR (0.5 pt) NSAID (0.5 pt) Subacromial Injection (0.5 pt)		
6	Operative Treatment (Max 2 pts)	Arthroscopic Repair (0.5 pt) Mini-Open Repair (0.5 pt) Subacromial Decompression (0.5 pt) Tendon Transfer (0.5 pt)		
7	Complications (Max 2 pts)	Recurrence/Repair Failure (0.5 pt) Prognosis (0.5 pt) Nerve Injury (0.5 pt) Infection (0.5 pt) Joint Stiffness (0.5 pt)		

RESULTS

The results of this study revealed that majority of the evaluated videos (40 videos, 70%) consists of general information about rotator cuff injuries. 12 videos were about treatment options (21%), 3 videos were lectures (5%) and remaining 2 videos classified as other (3%). Of the 57 videos evaluated, 43 (75.4%) were uploaded by health channels, 13 (22.8%) were uploaded by physicians, 1 (1.7%) was uploaded by other sources.

The mean video length was 402.68 seconds (144-1055 seconds), the mean number of views was 78840.98 (29-116740), the mean time since the video was posted was 1948.94 days (18-3975 days), the mean daily view rate was 41.96 (0.11-733 per day), the mean number of comments was 30.08 (0-428), the mean number of likes was 380.89 (0-5600), the mean number of dislikes was 29.05 (0-5236), and the mean VPI value was 91.92 (57.14-100). The mean scores for RCIA, JAMA and DISCERN were 3.63 (0.5-7.5), 3.05 (1-4) and 33.81 (21-56) respectively.

There was positive, weak, non-significant significant relationship between VPI and video source (r=0.107, p=0.517), positive, weak, insignificant relationship between VPI and RCIA (r=0.223, p=0.464) for physicians, positive, weak, signicant relationship between video length and JAMA (r=0.417, p=0.001) overall and positive, weak insignificant relationship between VPI and RCIA (r=0.049, p=0.765) for health channels.

DISCUSSION

The Internet is accepted as an unlimited source of information, but since almost none of the sources are peer-reviewed, the accuracy of the provided information is a big question. Patients have a growing tendency to investigate their medical conditions and treatment methods. YouTube is one of the most prominent online social media platforms, containing videos on virtually anything, including diseases and their treatment methods (8). Poor-quality health information may lead to false expectations, doctor-patient conflicts and cause mistrust. Recently, these topics were evaluated by other researchers. These studies stated that patients have some technical information about their diagnosis and treatment and that they can obtain this information from the internet (10). Although patients' access to this information is an advantage in terms of awareness, it has many disadvantages (11,12). We evaluated the videos in our study by searching YouTube for videos tagged with rotator cuff tears.

DISCERN and JAMA scores are validated scoring systems which were widely used in this kind of studies. On the other hand, these scores were not designed for video sources (DISCERN) and patient information media (JAMA). Therefore we used a novel and unvalidated scoring system, RCIA, specific to rotator cuff injuries. All aspects of rotator cuff injuries are covered including etiology, treatment and complications. Like similars in

the literature, we think that these kind of scoring systems are essential to evaluate informational media sources.

Considering the data in the literature, it was found that the videos with animation content and shorter duration were more liked and watched (13). In our study, we found that the videos that were shorter and shared by doctors were more liked by the audience. Similarly, Çelik et al. (14) found that video duration was negatively correlated with VPI but positively correlated with quality scores. In addition, we investigated whether there was a correlation between the liking rate and the quality of the videos, and it was determined that there was no significant correlation.

When we conducted a literature review, we discovered several recent studies evaluating the quality of videos used in the diagnosis and treatment of a variety of diseases. Each of these studies determined that the videos lacked a certain level of quality (15,16). In our study, 2 different researchers analyzed videos and scored their video quality using 3 different scoring systems. What the results all had in common was the poor informational quality of the videos. Although most of the videos were prepared by health institutions and a small portion by doctors, the video quality was similarly poor in both groups.

The main reason for the inadequate videos seems to be commercial concerns. Most of the videos were prepared according to the practice of the provider. Since there are no doctor-patient responsibility obligations, most of the providers do not feel obligated to inform the viewers of all aspects of the disease and treatment methods. This leads to a misunderstanding that a specific method could be the only solution. This lack of adequate information reaches its highest point in complications. There was almost no information about the complications patients might face during their treatments. The point that informational videos avoid informing about possible complications of the treatment modality was also mentioned in previous but other than rotator cuff studies (17,18).

Three of the videos included in our study were lectures, and they have the highest mean DISCERN (52) and RCIA (7.5) scores, but they also have the highest mean duration (894 sec.). These three videos have the lowest view rates. Although they are more informative than almost all the other videos, because of the length and amount of high-academic information they contain, viewers do not seem to prefer these videos. This tendency was also reported in a study by Kuru et al. (19) and found a negative correlation between video quality and number of likes which might reflect that high-quality videos are not as popular as low-quality videos.

When we analyzed the statistical results between the study parameters, we found that longer video length correlates only with structural data of the videos like JAMA quality score. Although interobserver reliability was found to be high for all three scoring systems, there was no correlation between the scoring systems.

Social media platforms are undeniable informational sources today. We think that health professionals and professional health organizations are responsible for developing a suitable way of providing adequate and true health information sources. This could be accomplished by creating a survey system like DISCERN for video sources and providing video-graphic content prepared for patients which includes all aspects of diseases, treatment choices and complications.

This study has some limitations. Only English language videos included in the study and limited to available videos on the exact search date. Number of included videos might be another limitation but since first 100 videos were scanned, this number is beyond the numbers of an average YouTube user search limits. Additionally, an unvalidated tool, RCIA score, used to evaluate content quality but high reliability may refer adequate design.

CONCLUSION

As a result, content quality of rotator cuff tear videos on YouTube is low. Physicians should inform the patients about insufficient and misleading information sources. Hippocrates stated, "There is no disease but the patient" and treatment methods are chosen based on the patient, not the disease. The correct choice of this treatment procedure depends on the physician-patient relationship with full informed consent. We believe that the patient's misunderstanding may jeopardize this relationship and lead patients to inappropriate treatments ending up with unwanted outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted as a YouTube research, there is no need for ethics committee approval.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

HEALTH SCIENCES
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How effective are body mass index and body muscle weight on cardiopulmonary resusitation?

Ejder Saylav Bora[1], Adem Çakır[2], Adnan Yamanoğlu[1]

[1]İzmir Atatürk Research and Training Hospital, Department of Emergency Medicine, İzmir, Turkey
[2]Başakşehir Çam ve Sakura City Hospital, Department of Emergency Medicine, İstanbul, Turkey

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ABSTRACT

Aim: The purpose of this study is searching the effect of BMI and BMW on the quality of CPR and the state of exhaustion applied by the professionals in the emergency department.

Material and Method: The software of the CPR education manikin was used in order to count and measure the number and the depth of the compressions and their correspondence to each other during the first and the second minutes of the procedure. Five cycles of chest compressions were asked to do from the rescurers. Each rescuer has handed the task of applying pressure over to his/her following team member after two minutes. Borg tiredness scores were asked to the rescuers and recorded at the end of each-minute period.

Results: The mean depth of pressure, the number of pressure attempts applied and the number of superficial compressions of the participants who were grouped due to their BMI showed no statistically meaningful difference. Both in the mean values of Borg tiredness scores which were calculated at the end of the first and second minutes; the group with lower BMW showed higher exhaustion significantly and this group couldn't make sufficient compressions by means of depth and number, and also the latter showed more exhaustion compared to the first.

Conclusion: It is considered that choosing the health workers who are going to apply CPR among individuals with higher BMW or encouraging the workers in those departmnets who frequently apply CPR to be more interested in sports activities could be a promoting factor for having good quality CPR and reducing mortality as well.

Keywords: Cardiopulmonary resuscitation, body mass index, body muscle weight, borg fatigue scale

INTRODUCTION

Cardiopulmonary arrest is the sudden and unexpected cessation of breathing and/or circulation in a patient for any reason. It is clinically defined as the absence of cardiac mechanical activity. The clinical diagnosis is confirmed by unresponsiveness, absence of pulse, and apnea. Practices that involve efforts to resuscitate a person whose life has been interrupted in any way are called Cardiopulmonary Resuscitation (CPR) (1,2). The 2020 AHA guideline draws attention to the importance of early recognition of cardiac arrest and early initiation of chest compressions by the rescuer (3).

High-quality chest compressions of at least 100-120 per minute in adult advanced cardiac life support, chest compression depth of at least 5-6 cm in adults. It is recommended to allow chest expansion after each compression, to reduce interruptions in compressions, to avoid overbreathing, and to change chest compressions every 2 minutes if more than one rescuer is present. There are not enough studies that draw attention to physical characteristics such as body mass index (BMI) or body muscle weight (BKA) of rescuers who will perform chest compressions. In addition, studies showing the effect of the victim's physical characteristics on chest compressions are also insufficient. This issue is not emphasized in the 2020 AHA guidelines (3).

Insufficient CPR quality was observed in studies conducted with nurses and nursing students (4). In a study examining the reasons for not performing adequate and effective chest compressions, weight, body mass index and female gender were found to be affecting factors. It is emphasized that individuals with higher body weight and body mass index perform more effective chest compression (5-9).

Corresponding Author: Ejder Saylav Bora, saylavbora@hotmail.com
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The aim of this study is to investigate the effects of body mass index and body muscle weight on CPR quality and fatigue of rescuers who professionally perform CPR in emergency services.

MATERIAL AND METHOD

The study was carried out with the permission of İzmir Katip Çelebi University Non-Interventional Clinical Researchs Ethics Committee (Date: 27.05.2021, Decision No: 281). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out between 01.05.2021 and 01.07.2021, by applying chest compression to the CPR manikin used for training purposes by emergency medicine residents working in a tertiary education and research hospital.

Using the software program of the CPR trainer dummy we used in our study, chest compressions applied by each rescuer were performed at 0-1.minute and 1-2.minutes. We calculated the number and depth of compressions as well as the number of superficial and appropriate chest compressions made by the practitioner in minute time intervals.

CPR rescue teams were formed in groups of two from 76 residents who participated in our study. Each rescue team was asked to apply chest compressions to the CPR trainer dummy for a total of 5 turns alternately. After each rescuer applied chest compressions for 2 minutes, he handed over the pressure application task to his teammate. The rescuers were asked and recorded their **Borg fatigue scale (BFS)** at the end of the 1st and 2nd minutes of each lap.

Segmented body analyzers are devices that work with the bio-impedance analysis method and measure by sending an electric current of 50 kilohertz (kHz) to the body. Measurements of 76 residents who participated in our study were made with a segmented body analyzer. As a result of the measurement, data such as body mass index, body muscle weight, body fat ratio were obtained. After the necessary measurements were made, the data of the normal weight and overweight groups were used according to the BMI classification of the World Health Organization. Eight (10.6%) of 76 resident physicians included in the study were not included in the study because they were in the obese group according to BMI classification and they were thought to distort the study data. The data of 68 residents who were suitable for the study were used.

Borg Fatigue Scale 1. BFS and scoring parameters

15- graduated scale		10- graduated scale	
6	No Fatigue	0	Not hard at al
7	fairly easy	0,5	Very very easy
8		1	Very easy
9	Very easy	2	easy
10		3	moderate
11	easy	4	
12		5	hard
13	A little hard	6	
14		7	Very hard
15	hard	8	
16		9	
17	Very hard	10	Very very hard
18			
19	pretty hard		
20	Maximum fatigue		

Since there is no classification method for body muscle weight (BMW), the median value of BMW of 67 residents was calculated and two groups were formed as those with high and low muscle weight.

In our study, the average number of compressions, average depth of compression, average number of appropriate compressions, average number of superficial compressions and fatigue were compared in a group of 67 residents divided into two using body mass index (BMI) and body muscle weight (BMW).

In our study, those with chest compression depth below 50 mm and above 60 mm were accepted as faulty compressions, and those with 50-60 mm were considered suitable compressions.

Statistical Analysis

Statistical analyzes were performed using SPSS version 15 software. The conformity of the variables to the normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were performed using median and interquartile ranges for non-normally distributed variables, and frequency tables for ordinal variables. Since there were non-parametric conditions, the variables were compared between groups using the Mann-Whitney U test. Cases where the P value was below 0.05 were considered as statistically significant results.

RESULTS

In this study if we evaluate demographic data; 64.7% of the 68 participants were male (n=44) and the mean age was 31.27±4.22 years. Parameters related to VCI and BMW values of the participants are given in **Table 1**. 64.7% of the participants were male and 35.3% were female. BMI and BMW were found to be significantly lower in women than in men. Both 1st and 2nd min of female cases. At the end of the study, it was seen that the mean score of the AQI was higher than that of the men (respectively, female ACS Scores were 1.min 12.59, while male ACS Points were 1.min 10.45; p=0.016; female ACS Points were 2.min 13.01, while male ACS Points were 2.min 11, 59; p=0.038). It was found that women were significantly more tired than men.

Table 1. Demographic characteristics of the participants participating in the study

Parametre	Male	Female	p	Total
Number of participant (%)	44 (64.7)	24 (35.3)	-	68 (100)
Average on age (±ss) (yıl)	32.19±4.53	30.23±2.59	0.218	31.27±4.22
BMI Median	26.14	21.11	<0.001	24.43
BMW Median	36.43	23.58	<0.001	33.89
BMI			0.098	
Normal (n (%))	22 (56.4)	17 (43.6)		39 (100.0)
High (n (%))	22 (75.8)	7 (24.2)		29 (100.0)
BMW			0.008	
Low (BMW <33,91) (n (%))	10 (22.7)	24 (77.3)		44 (100.0)
High BMW ≥33,91 (n (%))	34 (100.0)	0 (0.0)		34 (33.0)

When the ages of the cases and the quality of CPR were examined; It was observed that the BCS score increased significantly with increasing age (p<0.001), but the rate of incorrect compression decreased with increasing age (p=0.026). This shows that while experienced health personnel make fewer false presses, fatigue occurs faster with increasing age.

Participants were divided into high and normal groups according to their BMI values, and the parameters measured in these participants were analyzed. The average compression depth of the participants grouped according to BMI, the number of compressions at the end of the 1st and 2nd minutes, and the 1st and 2nd min. There was no statistically significant difference between the mean pressure errors measured at the end of the study. Both 1st and 2nd min. On the other hand, in the mean BCS scores measured at the end of the study, it was found that patients with a high BMI had significantly less fatigue (**Table 2** and **Figure 1**).

According to the BMW values of the participants, they were analyzed in two groups as high and low. The parameters measured in these participants were analyzed and the analysis results obtained are given in **Table 3**. It was observed that there was a statistically significant difference in all parameters measured for CPR compliance of the participants grouped according to BMW. According to these parameters, it was determined that the participants with low BMW could not create enough compressions, the number of incorrect compressions increased afterward, and they were more tired compared to the BCS score data (**Table 3**, **Figure 2**).

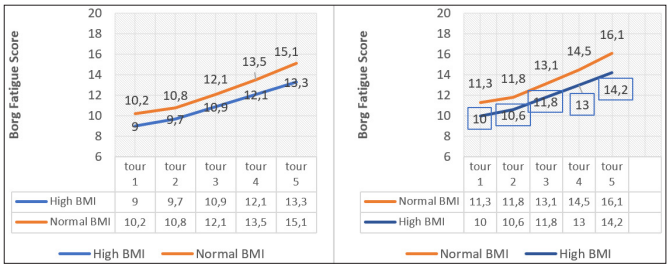

Figure 1. Comparison of BFS Score at the end of 1st and 2nd minutes in cases with normal and high BMI. **a.** 1st minute BFS Score **b.** BFS Score at the end of the 2nd minute

Table 2. Analysis of CPR parameters measured at the end of 1st and 2nd minutes of participants with normal and high BMI

Parametre For 5 Rounds of CPR	High BMI Mean±Ss (n=28)	Normal BMI Mean±Ss (n=40)	p*
Average Compression Depth (mm)	57.48±5.52	56.38±6.84	0.463
Number of Appropriate Presses (0-1. Min)	115.42±21.88	110.31±27.34	0.516
Number of Appropriate Presses (1-2. Min)	108.52±31.25	89.68±42.28	0.208
Incorrect Compression Average (0-1. Min)	12.15±23.92	20.14±26.52	0.498
Incorrect Compression Average (1-2. Min)	17.50±33.23	40.32±37.25	0.121
BFS Average Score (end of 1. min)	10.99±1.68	12.42±1.54	0.007
BFS Average Score (end of 2. min)	11.95±1.72	13.28±1.53	0.006

*Mann-Whitney U Test used

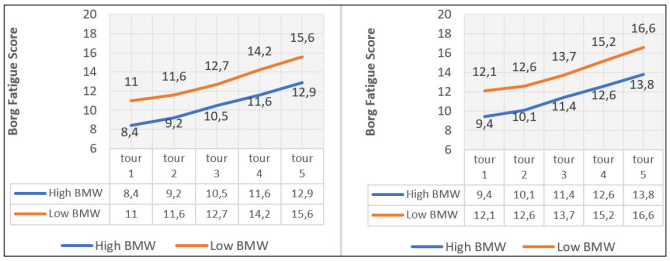

Figure 2. Comparison of BFS Score at the end of 1st and 2nd minutes in cases with high and low VKA. **a.** 1st minute BFS Score **b.** BFS Score at the end of the 2nd minute

Table 3. Analysis of CPR parameters measured at the end of 1st and 2nd minutes of BMW high and low cases

Parametre For 5 Rounds of CPR	High BMW Mean±Ss (n=34)	Low BMW Mean±Ss (n=34)	p*
Average Compression Depth (mm)	59.22±4.04	53.19±6.55	0.004
Number of Appropriate Presses (0-1. Min)	124.89±13.02	100.28±27.59	0.002
Number of Appropriate Presses (1-2. Min)	122.92±11.26	74.88±40.76	>0.001
Incorrect Compression Average (0-1. Min)	3.68±4.24	29.78±29.86	0.001
Incorrect Compression Average (1-2. Min)	6.24±9.51	51.8±46.25	<0.001
BFS Average Score (end of 1. min)	10.29±0.84	12.99±1.48	<0.001
BFS Average Score (end of 2. min)	11.25±0.82	13.18±1.60	<0.001

*Mann-Whitney U Test used

DISCUSSION

Recently, the importance of both efficiency and time in CPR applications has become well understood. In addition, devices have been introduced in many CPR applications and continue to be used actively (10). In addition, the human factor on CPR is still emphasized. For this reason, factors affecting the effectiveness of healthcare professionals in CPR are being investigated (11). A few of these are BMI and BMW.

Examining the effect of physical fitness on chest compression, Ock et al. (12) measured the physical fitness parameters of the participants, such as maximal aerobic exercise capacity, muscle strength, and muscular endurance, and asked the participants to press the CPR trainer dummy continuously for 5 minutes.

Ock et al. (12) found that the percentage of correctly applied chest compressions decreased significantly after the first minute, and this percentage decreased continuously as the duration increased. However, they revealed that the number of correctly applied chest compressions was also related to muscle strength. Based on the research findings, Ock et al. (12) stated that exercise programs that increase muscle strength are important and necessary for CPR practitioners and for increasing the quality and effectiveness of CPR applied after cardiac arrest.

In our study, according to BMW, the fatigue of the participants at the end of the CPR period at the end of the 1st and 2nd minutes was less in the participants with high BMW compared to the participants with low BMW, chest compression was higher in participants with high BMW, and appropriate chest compression was observed. It was observed that the number of BMW decreased in cases with low BMW and these numbers remained below the optimum desired numbers for CPR. Considering these results, it was seen that patients with low BMW could not complete even 1 cycle of 2 minutes of CPR while performing CPR, and it would be beneficial if a certain limit was set for BMW in CPR practice, and it would be beneficial to plan for the personnel performing CPR to participate in sports activities at regular intervals. was considered.

Another important finding obtained as a result of the study is that the chest compression is at superficial depth. Results 0-1 of rescuers with low BMW. and 1-2. showed that the number of superficial chest compressions applied between 1 and 2 minutes was significantly higher than the number of superficial chest compressions applied by rescuers with high BMW ($p=0.001$ and $p<0.001$, respectively).

Some studies on the quality of chest compression have revealed that the compression is superficial. In the study conducted by Wik et al. (13) with ambulance personnel in 2005, they found that chest compressions could not be applied in half of the pre-hospital interventions applied to 176 adult patients, and most of the chest compressions applied were at a superficial level. Similarly, in the study conducted by Abella et al. (14) on 67 patients who underwent CPR by equipped and trained hospital personnel in the hospital, they revealed that 37% of the chest compression applied was superficial (<38 mm.) (14).

Alspach, in his study on the quality of CPR in which he compared various studies, emphasized that chest compressions applied within the scope of CPR were applied superficially and below the recommended depth (15). Another finding on the quality and effectiveness of chest compression, one of the CPR parameters, was revealed in a study conducted by Brennan and Braslow in 1998. In a study conducted with 226 trainees participating in CPR trainings given by the American Red Cross and the American Heart Foundation, it was found that 50% of the participants applied chest compressions correctly at a rate of 2%, and that most of the incorrectly applied chest compressions were caused by insufficient depth (16).

In the study conducted by Zhang et al. (17) in 2013 with the participation of 219 health personnel, it was revealed that one of the important factors affecting the quality of chest compression is gender. In the study, in which 77 male and 142 female healthcare professionals were applied, 2-minute chest compressions were applied on the manikin, it was determined that the average of the number of appropriate chest compressions and deep chest compressions of male participants was higher than that of female participants. In their research, they emphasized that the quality of chest compressions of female health personnel is lower than that of men. In addition, it was determined that female personnel received higher ACO scores than males and were more tired compared to this scoring.

In a study conducted by Lucia et al. (18) in 1999 examining the effect of the physical fitness of the rescuer on adequate CPR performance, 14 professional CPR rescuers with a sedentary lifestyle and 14 physically active rescuers inexperienced in CPR practice were put on a CPR trainer dummy for 18 minutes uninterrupted. compared chest compression application. As a result of the study, it was revealed that 4 people in the sedentary group could not complete the application due to pain and physical fatigue in the upper extremity, and they stated that a certain level of physical fitness of CPR rescuers is necessary and beneficial in order to maintain the effectiveness and quality of CPR in long applications.

In a systematic review examining simulation-based learning in nursing education, Cant and Cooper (19) and Sanchez (20) emphasized that simulation with medium

and/or high reliability using a manikin is effective in teaching and learning when the practice guidelines are adhered to.

In an observational study conducted by Hokenek and Erdoğan (21) the results of thorax CT performed after cpr performed on non-traumatic cardiac arrest patients were compared and it was determined that the intrathoracic volume decreased in traumas secondary to cpr. Considering that patients with high BMI and BMW have a high risk of causing thoracic trauma in our study, we shouldnt forget that the important thing in CPR is not the weight and strength of the practitioner, but the speed and depth of compression in accordance with the recommendations of AHA 2020.

As a result, it was seen that BMW and BMI were important factors in the effectiveness of CPR in healthcare workers. It was observed that healthcare workers with high BMI and high BMI were less tired than those with low BMI. While no significant differences were observed in CPR parameters in BMI cases, it was observed that the number of appropriate compressions was significantly higher and the number of false compressions was lower in cases with high BMW. Again, it was seen that male participants had less fatigue than females and the fatigue was higher as the age increased.

CONCLUSION

It was thought that choosing the healthcare worker to perform CPR from people with high BMW or encouraging healthcare professionals working in units with frequent CPR to increase BMW through sports activities would increase the quality and effectiveness of CPR and pave the way for a decrease in mortality rates..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Katip Çelebi University Non-Interventional Clinical Researchs Ethics Committee (Date: 27.05.2021, Decision No: 281).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

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The relationship between non-alcoholic fatty liver disease and breast cancer: a retrospective case-control study

Sevde Nur Fırat[1], Abdullah Durhan[2], Serap Erel[3], Cavit Çulha[1]

[1]University of Health Sciences, Ankara Training and Research Hospital, Department of Endocrinology and Metabolism, Ankara, Turkey
[2]University of Health Sciences, Ankara Training and Research Hospital, Department of Surgical Oncology, Ankara, Turkey
[3]University of Health Sciences, Ankara Training and Research Hospital, Department of General Surgery, Ankara, Turkey

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ABSTRACT

Aim: Breast cancer is the most common cancer among women and is one of the main causes of death in women. It is known that some metabolic components that are risk factors for non-alcoholic fatty liver disease are also risk factors for breast cancer. The aim of this retrospective cohort study was to show the prevalence of non-alcoholic fatty liver disease breast cancer patients and the effect of non-alcoholic fatty liver disease on breast cancer development through comparisons with a control group with normal mammography.

Material and Method: The study included 108 patients who were operated on for breast cancer in the general surgery clinic of our hospital between January 2015 and December 2018 and who underwent abdominal ultrasound for breast cancer staging. A control group was formed of 102 women with benign breast lesions on routine mammography and who underwent abdominal ultrasound within 6 months before mammography. The prevalence of diabetes, hypertension and hyperlipidemia and body mass indexes were similar in both groups.

Results: In the evaluation of all the study participants, an association was found between non-alcoholic fatty liver disease and breast cancer. In the obese and non-obese subgroups, non-alcoholic fatty liver disease was significantly associated with breast cancer in the non-obese subgroup. [OR 2.67%, 95% confidence interval [95% CI) 1.1-6.0, p=0.020].

Conclusion: Non-alcoholic fatty liver disease was seen to be significantly associated with breast cancer regardless of known risk factors. This relationship there was in non-obese women with NAFLD, but not in the obese group.

Keywords: Breast cancer, nonalcoholic fatty liver disease, non-obese women, obesity

INTRODUCTION

Breast cancer is important because it is the most common cancer type in female population and one of the main causes of deaths associated with cancer among women (1). Late age in menopause, early menarche, hormonal or reproductive factors, family history, late pregnancy, and nulliparity are certain risk factors for this disease (2,3). Recent meta-analyses have also shown an association of metabolic syndrome components and obesity with an increased breast cancer risk (4).

There is an association between non-alcoholic fatty liver disease (NAFLD) and such factors as metabolic abnormalities and obesity. NAFLD is an increasingly widespread clinical condition and an important health problem because it may progress to cirrhosis, non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma, and end-stage liver disease. Recent studies have shown that NAFLD may be an additional risk factor for non-hepatic cancers in the gastrointestinal tract (5,6). However, there are few studies in the literature on the relationship of NAFLD with breast cancer (7,8).

Mammography is the most effective method for breast cancer screening. Liver biopsy is known as the gold standard for NAFLD diagnosis; however, its use in clinical practice is limited since it is an invasive test. Ultrasound is an accurate imaging method, which is used to help detect and characterize hepatic steatosis (9).

This study is aimed at determining the relationship of NAFLD with breast cancer.

Corresponding Author: Sevde Nur Fırat, sevdenursuruc@yahoo.com
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MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ankara Training and Research Hospital Clinical Researchs Ethics Committee (Date: 17.09.2020, Decision No: 20-367). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included the data obtained from 108 breast cancer patients who were operated on in the Department of General Surgery between January 2015 and September 2018. A control group was formed of 102 women with benign breast masses detected on mammography. The study exclusion criteria included having autoimmune hepatitis, chronic viral hepatitis B/C, significant alcohol consumption (140 g/week) and other chronic liver diseases. A record was made for each patient of the clinical, anthropometric, radiological and laboratory data. The following formula was utilized to calculate the BMI of the patients: weight (kg/height square m2). Those with BMI ≥30 were considered obese. Laboratory studies included alanine aminotransferase (ALT), fasting blood glucose, and serum aspartate aminotransferase (AST). Patients with >3-fold the upper limit of normal for AST and/or ALT were defined as liver damage and these patients were also excluded. Molecular subtypes of breast cancer (luminal A, luminal B, HER2 +, and triple negative), tumor size, and Ki-67 indices were obtained from the hospital database. Breast cancer subtypes were grouped as follows; Luminal A; Patients with positive/exhibiting ER and PR receptors, Luminal B; It includes ER and PR receptors positive/exhibiting and higher histological grade than Luminal A, triple negative (ER, PR and HER-2 negative/non-exhibiting) group.

Fatty liver disease was evaluated according to the reports of abdominal ultrasonography performed for staging when breast cancer was diagnosed. For control subjects with benign breast masses, the abdominal ultrasonography reports taken within six months of the mammography were recorded. The mammographies were evaluated in line with the Breast Imaging Reporting and Data System (BI-RADS). According to this tool, category-1 includes negative and category-2 benign findings. Possibly benign findings are included in category-3. Findings in category-4 are labeled as suspicious for malignancy. Finally, category-5 is for findings that are highly significant malignancy10. Patients with BI-RADS 1, 2, and 3 mammographies were included in the control group.

The study data were statistically analyzed through SPSS version 21. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used in order to assess conformity of the data to normal distribution. Descriptive statistics for continuous variables were stated as mean±standard deviation and minimum-maximum values. The statistical significance of the difference in categorical variables between the study groups was evaluated with the Chi-square test. The mean differences between the groups were compared with One-Way ANOVA. When parametric test assumptions were not met, the comparison of both ordered data and continuous variables was performed using the Mann-Whitney U test. Finally, multivariate logistic regression analysis was used to analyze how fatty liver affected breast cancer. All tests applied had two tails; moreover, statistical significance was designated as $p<0.05$.

RESULTS

Of the 210 patients included in the study, benign breast disease was determined in 102 (48.5%) with a mean age of 54.5±11.6 years, and breast cancer was determined in 108 (51.50%) with a mean age of 52.4±10.1 years. **Table 1** shows the clinical and demographic characteristics of the two groups. Age, BMI, the prevalence of HT, DM, HL and AST, ALT and glucose levels were similar in both groups.

Table 1. Demographic, clinical and laboratuary characteristics of the study participians

Characteristics	Control (n:102)	Breast cancer (n:108)	p value
Age, mean, years	52.4 (±10.1)	54.5 (±11.6)	0.157
BMI, mean, (kg/m2)	29.6 (±4.8)	29.2 (±4.8)	0.845
DM, n (%)	21 (20.5)	18 (16.6)	0.465
HT, n (%)	22 (21.5)	22 (20.3)	0.831
HL, n (%)	13 (12.7)	11 (10.1)	0.560
NAFLD, n (%)	30 (29.4)	48 (44.4)	0.025*
Glucose, mean±SD, (mg/dl)	106 (±30.9)	103.1 (±27.3)	0.224
ALT (IU/L), mean	17.8 (±7.2)	18.1 (±9.1)	0.891
AST(IU/L), mean	19.2 (±6.8)	18.8 (±5.8)	0.899

BMI=body mass index, DM=diabetes mellitus, HT=hypertension, HL=hyperlipidemia, ALT=alanine transaminase, AST=aspartate transaminase.* statistical significance, $p<0.05$

In the breast cancer group, NAFLD prevalence was 44.4% (48/108), which was significantly higher than the control (29.4%, 30/102) (p=0.025). The subgroup analysis revealed that fatty liver was linked with breast cancer occurrence in the non-obese group, but NAFLD and breast cancer were not associated in the obese group (p=0.014, p=0.336, respectively). Multivariate analysis showed that in the total study population a significant association existed between NAFLD and breast cancer [odds ratio (OR) 1.92%, 95% confidence interval (95%CI) 1.0–3.3, (p=0.025)]. When the patients were evaluated as obese and non-obese, NAFLD was found to be statistically significantly related to breast cancer in the non-obese subgroup [OR 2.67%, 95% confidence interval (95%CI) 1.1–6.0, p=0.020] (**Table 2**). No significant association was revealed in the obese group (p=0.337) between NAFLD and breast cancer.

Table 2. Results of the multivariate analysis		
	OR (95% CI)	p value
Total population NAFLD	1.92 (1.0-3.3)	0.025*
Nonobese group NAFLD	2.67 (1.1-6.0)	0.020*
NAFLD: Non-alcoholic fatty liver disease		

Invasive ductal carcinoma (85.2%) was the most common pathological subtype in breast cancer patients. Tumor diameter was approximately 2.5 cm. There was lymph node metastasis in 38% of the patients and the tumor was unifocal in 86.1%. The mean value of the Ki-67 index was 15.09±12.9.

In the molecular subtype staging of the patients, 39 (36.1%) were luminal A, 32 (29.6%) were luminal B, 36(33.3%) were HER-2 positive, and 1(0.9%) was triple negative. The evaluation of all the patients could not find out any statistically significant differences between the presence of NAFLD and molecular subtypes. In the evaluation of the subgroup of obese patients, the presence of NAFLD was higher in the luminal B group than the luminal A group, which was statistically significant (p=0.042) (**Table 3**). Also, at the end of the evaluation of the relationships between NAFLD and histological subtype of breast cancer, there were no significant differences between the presence of NAFLD and histological subtype. There was no significant relationship between Ki-67 indexes and NAFLD.

In the control group, 4 (3.9%) patients were BI-RADS-1, 46 (45.1%) were BI-RADS-2, and 52 (51%) were BI-RADS-3. No significant association was detected between the BI-RADS score of the patients and NAFLD (p=0.316).

DISCUSSION

According to the results of this study, which compared the relationship of NAFLD with breast cancer in patients and controls, NAFLD is related to breast cancer independently of known risk factors. Moreover, there was a relationship between the presence of NAFLD and breast cancer in the non-obese subgroup.

Despite the widespread use of breast cancer screening methods and developing technology, it is still the most frequent type of cancer and the leading death cause for women. Most commonly known controllable risk factors for breast cancer include genetics, diet, lifestyle, hormone replacement therapy, alcohol consumption and obesity (1,11,12). Based on these factors, there are numerous studies showing that breast cancer is associated with obesity, metabolic syndrome, and diabetes (6,13). Moreover, these factors are also known risk factors for NAFLD. Dyslipidemia, sleep apnea, family history, hypothyroidism, hypogonadism, and sedentary lifestyle are other factors in NAFLD etiology (14). The common metabolic risk factors of breast cancer and NAFLD suggest a potential relationship between these two diseases. Another important factor in NAFLD physiopathology is insulin resistance due to obesity. Excessive fatty acids accumulating in the cell with insulin resistance cause an increase in oxidative stress parameters and a decrease in antioxidants. This situation causes mitochondrial dysfunction, uncontrolled cytokine release, especially TNF-alpha, increased IL-8 and necroinflammation. There is a decrease in adiponectin, which is known to be an anti-inflammatory, anti-TNF and liver-protective cytokine. Decreased adiponectin levels lead to significant insulin resistance, followed by increased insulin levels and growth factor-1 (IGF-1), which bind to its receptors in the cell, causing cell proliferation and increased vascular endothelial growth factor production (15,16). Another reason is the high leptin levels in the blood, which both increase insulin resistance and affect the development of carcinogenesis. In recent years, many studies have been conducted on different types of cancer related to inflammation and cancer development (17,18).

NAFLD is known to cause liver, heart and kidney diseases, and many studies on the risk of extrahepatic malignancy have reported a relationship between NAFLD and some types of cancer (19,20). However, there are few studies in the literature on the association of NAFLD with breast cancer. Kwak et al. (8) reported a statistically significant difference in NAFLD between non-obese breast cancer patients and a control group, similar to our study. Nseir et

Table 3. Relationship between NAFLD and breast cancer molecular subtypes					
	Luminal A	Luminal B	HER-2 positive	Triple negative	p value
Total breast cancer					
NAFLD, n (%)	15 (31.2)	16 (33.3)	17 (35.4)	-	
No NAFLD, n (%)	24 (40)	16 (26.6)	19 (31.6)	1 (1.66)	0.598
Obese group				-	
NAFLD n (%)	7 (21.2) [a]	12 (36.3)[a]	4 (12.1)		
No NAFLD, n (%)	11 (55)	3 (15)	6 (30)		0.042*
Nonobese group					
NAFLD, n (%)	8 (32)	4 (16)	13 (52)	-	
No NAFLD, n (%)	13 (32.5)	13 (32.5)	13 (32.5)	1 (2.5)	0.304
[a]statistical significance, p<0.05, group luminal A vs group luminal B.					

al. (7) showed that NAFLD and estrogen use are predictive factors for breast cancer. Lee et al. (21) also showed that NAFLD is a predictive factor in terms of breast cancer and a prognostic factor for its recurrence. In our current study, when breast cancer and benign breast patients were compared, NAFLD was found to be statistically higher in breast cancer patients (44.4% vs 29.4%) (p=0.024). In addition, when divided into subgroups, NAFLD was found to be statistically considerably higher among patients with breast cancer within the non-obese group. This particular finding is important because it shows that NAFLD may be associated with breast cancer independently of obesity. The current study results were not statistically significant when breast cancer cases were compared according to hormone receptor positivity and ki-67 index to define the mechanical relationship with NAFLD. Similar to the current study, Kwak et al. reported no significant relationship between hormone receptor positivity and NAFLD (8).

Liver biopsy constitutes the gold standard for NAFLD diagnosis, but since it is an invasive test and cannot be routinely applied to every patient, the patients selected for this study were those with hepatobiliary ultrasound, as a non-invasive imaging method (22). In literature, ultrasonography and tomography examinations have been mostly preferred (7,8,23). NAFLD may be a risk factor for cancer disease or may develop depending on treatment such as chemotherapy and endocrine therapy. NAFLD has been described in case reports of patients with breast cancer due to tamoxifen (24). Tamoxifen leads to hepatic fatty liver by raising serum triglycerides, activating the b-oxidation pathway, and suppressing the synthesis of estrogen (25). Therefore, breast cancer patients with NAFLD who are receiving endocrine therapy should be followed closely due to the risk of recurrence and increased morbidity.

This study was a single-centered, retrospective one with a small sample size of 210 patients, which were the main limitations. Our study was retrospective, therefore, it is difficult to say that the presence of NAFLD is a independent risk factor for the development of breast cancer. The diagnosis of NAFLD was made with USG, which is a non-invasive imaging method, rather than biopsy. It can be recommended that future studies could use magnetic resonance imaging, which is a non-invasive test with high sensitivity and specificity.

CONCLUSION

In this study, an association was found between NAFLD and breast cancer. This association was also present in the non-obese population with NAFLD. These results are important in showing that the may be associated with the development of breast cancer in both obese and non-obese women with NAFLD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ankara Training and Research Hospital Clinical Researchs Ethics Committee (Date: 17.09.2020, Decision No: 20-367).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Does preoperative vitamin D deficiency delay recovery time from transient hypocalcemia after thyroidectomy?

Tezcan Akın[1], Umut Fırat Turan[2], Sadettin Er[1], Sabri Özden[3], Mesut Tez[4], Barış Saylam[4]

[1]Ankara City Hospital, Department of General Surgery, Ankara, Turkey
[2]Kahramankazan Public Hospital, Ankara, Turkey
[3]Konya City Hospital, Department of General Surgery, Konya, Turkey
[4]Health Sciences University Ankara City Hospital, Department of General Surgery, Ankara, Turkey

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ABSTRACT

Aim: To investigate the relationship between preoperative vitamin D deficiency and the recovery/healing time from postoperative hypoparathyroidism or hypocalcemia.

Material and Method: The sample consisted of patients that underwent thyroidectomy and preoperative 25-hydroxy-vitamin D analysis between 2014 and 2018 at the General Surgery Clinic of Health Sciences University Ankara Numune Training and Research Hospital. Of the 1598 patients who underwent total thyroidectomy, 73 were included in the study. These patients were selected from 214 patients who developed postoperative hypocalcemia. The patients' demographic characteristics, surgical indications, operative findings, postoperative pathology results, preoperative and postoperative biochemical parameters and clinical outcomes were retrospectively obtained from the electronic records.

Results: Of the 73 patients included in the study, 10 (13.7%) were male and 63 (86.3%) were female. Preoperative vitamin D level was normal in 16 patients and deficient in 57. The patients were divided into two groups: Group 1 with normal preoperative vitamin-D levels and Group 2 with vitamin D deficiency. There was no statistically significant difference between Groups 1 and 2 in terms of parathormone (months 1, 2 and 3) and calcium levels ($p>0.05$); however, preoperative vitamin D levels statistically significantly differed between the two groups.

Conclusion: Our study suggests that having a normal level of vitamin D or deficiency does not have significant effect on the recovery time from hypocalcemia after thyroidectomy. Therefore, we consider that it is not necessary to measure vitamin D in routine preoperative screening or apply a vitamin D replacement.

Keywords: Preoperative vitamin D level, transient hypocalcemia, postoperative parathormone level

INTRODUCTION

Hypoparathyroidism and hypocalcemia are well-known complications after thyroidectomy (1). However, most studies on the improvement of parathyroid function after thyroidectomy have a limited sample size or report the outcomes over a short observation period after surgery (2). Some researchers found that the recovery time of parathyroid function after thyroidectomy may take more than one year (3). This duration is becoming longer in parallel to the increased incidence of thyroid cancer observed in recent years (4). In the literature, the risk of developing this complication has been determined to vary between 1 and 50% (5).

In Turkey, of the population living in different regions, more than 30% have vitamin D deficiency (6). Low vitamin D induces calcium absorption by increasing calcium reabsorption in the kidney. This may result in increased parathormone (PTH) levels and compensatory hyperparathyroidism, which maintain normal calcium levels (7). Most patients who develop postoperative hypocalcemia recover within a few months, but the course of symptomatic hypocalcemia may be catastrophic since it can lead to prolonged hospitalization or re-hospitalization (8).

Post-thyroidectomy hypocalcemia is the most common complication of thyroidectomy and can cause transient or permanent hypocalcemia(9). Despite many studies investigating postoperative hypocalcemia, conflicting results have been obtained concerning the effect of preoperative vitamin D deficiency on postoperative

Corresponding Author: Tezcan Akın, drtezcanakin@gmail.com
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hypocalcemia (10). Some researchers have shown that vitamin D deficiency is correlated with postoperative hypocalcemia, and thus require a longer hospital stay (11). The best indicator of Vitamin D status in tissues is serum 25-hydroxyvitamin D level(12) .Various cut off values for vitamin D deficiency have been accepted by different organizations and authors (13). Vitamin D deficiency, which is a global health problem, is generally defined as serum 25-hydroxyvitamin D levels less than 20 ng/mL (14). In studies undertaken in Turkey, the optimal values for vitamin D have also been accepted as >20 ng/ml (15). In this study, we aimed to investigate the association between vitamin D deficiency and the recovery time from postoperative hypoparathyroidism and hypocalcemia.

MATERIAL AND METHOD

Patient Data

In this study, the data obtained from the electronic records of all patients who underwent thyroidectomy between 2014 and 2018 at the General Surgery Clinic of Ankara Numune Training and Research Hospital were retrospectively utilized. This retrospective study was approved by Health Sciences University, Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 28.03.2019, Decission No: E.Kurul-E-19-2631/2631). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Of the 1598 patients who underwent total thyroidectomy, 73 were included in the study. These patients were selected from 214 patients who developed postoperative hypocalcemia. The demographic features, surgical indications, operative findings, postoperative pathology results, preoperative and postoperative biochemical parameters, and clinical outcomes of the patients were noted. Only patients for whom a preoperative 25-hydroxy-vitamin D analysis was undertaken and who developed hypocalcemia after thyroidectomy were included in the study. Vitamin D deficiency was defined as vitamin D levels of <20 ng/mL. In addition, the postoperative thresholds were accepted as <8 mg/dl for serum calcium levels and <14 pg/ml for PTH (PTH reference values of our hospital: 15-65 pg/ml) (16). Normal parathyroid function was defined as a normal PTH value in asymptomatic patients who did not require replacement therapy. Excluded from the study were patients with chronic kidney disease or history of parathyroidectomy, those supplemented with calcium or vitamin D, and those who underwent surgery due to a recurrent benign or malignant disease and patients who underwent thyroidectomy for primary hyperparathyroidism. There were no patients with permanent hypoparathyroidism that matched the specified criteria.

Statistical Analysis

All data were analyzed using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). The data of continuous variables were given as mean±standard deviation (SD). Categorical data were obtained as frequency with percentages. The Mann-Whitney U test was used to compare the continuous variables depending on data distribution, and the chi-square test or Fisher's exact test was employed for categorical variables. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 73 patients included in the study, 10 (13.7%) were male and 63 (86.3%) were female. The median (IQR) age was 49 (38-55) years. The preoperative vitamin D level was normal in 16 patients and deficient in 57. The patients were divided into Group 1 with normal preoperative vitamin D levels and Group 2 with vitamin D deficiency. The indications for thyroidectomy were as follows: nodular goiter in 47 patients (64.4%), differentiated thyroid cancer+undifferentiated thyroid cancer in 21 patients (28.8%), Graves' disease in one patient (1.4%), and toxic multi-nodular goiter in four patients (5.5%). The types of operation performed were thyroidectomy (n=50; 68.5%), thyroidectomy+central lymph node dissection (CLND) (n=15; 20.5%), completion thyroidectomy (n=1; 1.4%), and thyroidectomy+CLND+lateral neck dissection (n=7; 9.6%) (**Table 1**). The median (IQR) value of incidental parathyroid excision was 0.0 (0-1). The mean duration of hospitalization was 3.95 (1-14) days.

Table 1. Features of the patients

Feature	n (%)
Sex	
Male	10 (13.7)
Female	63 (86.3)
Age- Median (IQR)	49 (38-55)
Indication	
Nodular Goiter	47 (64.4)
DTC and UDTC	21 (28.8)
Graves' Disease	1 (1.4)
Toxic MNG	4 (5.5)
Operation type	
Thyroidectomy	50 (68.5)
Thyroidectomy +CLND	15 (20.5)
Completion Thyroidectomy	1 (1.4)
Thyroidectomy +CLND +LND	7 (9.6)
Excised Parathyroid count- Median (IQR)	0.0 (0-1)
Hospital stay (day)- Mean (Min-Max)	3.95 (1-14)

IQR: Interquartile range, DTC: Differentiated thyroid cancer, UDTC: Undifferentiated thyroid cancer, MNG: Multi-nodular goiter, CLND: Central lymph node dissection, LND: Lateral neck dissection.

Table 2 presents the demographic distribution of the patients in Group 1 (n=16) and Group 2 (n=57). The PTH values at postoperative months 1, 2 and 3 were 16.50 (10.80-33.60), 22.45 (12.30-43.60) and 25.75 (13.05-38.30), respectively for Group 1 and 19 (10.55-30.25), 23.20 (13.20-32.20) and 25.95 (19.80-35.40), respectively for Group 2. The calcium values at postoperative months 1, 2 and 3 were measured as 9.16 (8.73-9.57), 8.90 (8.21-9.26) and 8.7 (8.12-9.25), respectively for Group 1 and 8.81 (8.25-9.48), 8.54 (8.14-9.14) and 8.76 (8.18-9.09), respectively for Group 2. There was no statistically significant difference between Groups 1 and 2 in terms of PTH (months 1, 2 and 3) and calcium levels in the postoperative period (p>0.05). However, the preoperative vitamin D level statistically significantly differed between the two groups (**Table 3**).

Table 2. Patient characteristics according to groups

	Normal Vitamin D Levels Group 1 n (%)	Vitamin D Deficiency Group 2 n (%)
Sex		
Male	1 (6.3)	9 (15.8)
Female	15 (93.8)	48 (84.2)
Age- Mean (IQR)	46 (32.5-59)	49
Indication		
Nodular Goiter	12 (75)	35 (61.4)
DTC and UDTC	4 (25)	17 (29.8)
Graves' Disease	0 (0)	1 (1.8)
Toxic MNG	0 (0)	4 (7)
Operation Type		
Thyroidectomy	11 (68.8)	39 (68.4)
Thyroidectomy +CLND	2 (12.5)	13 (22.8)
Completion Thyroidectomy	0 (0)	1 (1.8)
Thyroidectomy +CLND +LND	3 (18.8)	4 (7)
Excised Parathyroid Count-Median (IQR)	0.50 (0-1.50)	0 (0-1)
Hospital Stay (day)-Mean (Min-Max)	3 (2-4)	4 (2-5)

IQR: Interquartile range, DTC: Differentiated thyroid cancer, UDTC: Undifferentiated thyroid cancer, MNG: Multi nodular goiter, CLND: Central lymph node dissection, LND: Lateral neck dissection.

DISCUSSION

Recently, many studies have been conducted to determine the preoperative factors predicting the development of hypocalcemia after thyroidectomy. The causes of hypocalcemia after thyroidectomy are multifactorial, including injury, devascularization, inadvertent excision of parathyroid glands, number of remaining functional glands, scope of surgery, experience of the surgeon, hyperthyroidism, retrosternal goiter, concurrent neck dissection, and thyroid carcinoma (17). During thyroidectomy, incidental parathyroidectomy is not uncommon. Almost half of the parathyroid glands are intrathyroidal, and therefore iatrogenic parathyroidectomy is inevitable (18). The question of how many parathyroid glands should be preserved to maintain normal serum calcium levels remains controversial. Several studies claimed that a single functional gland is sufficient for normal parathyroid activity, but other researchers recommended preserving at least three glands (19, 20).

In the literature, there is also no consensus on how to best define the recovery of parathyroid gland function. Some studies consider a euparathyroid state even in the absence of hypocalcemia symptoms if the serum PTH levels rise to at least 10 pg/mL (2). At the same time, it can be stated that the function of the parathyroid gland is improved when therapeutic calcium or calcitriol supplements are no longer required to prevent hypocalcemia symptoms. Another way of defining the improvement of parathyroid gland function is based on the serum PTH level being within the normal range.

Vitamin D, PTH and calcitonin have a critical role in calcium homeostasis. Therefore, the serum vitamin D level after thyroidectomy is expected to be associated with hypocalcemia; however, this assumption remains controversial (21). For example, some authors reported that preoperative vitamin D deficiency was responsible

Table 3. Laboratory parameters of patients according to groups

	Normal Vitamin D Levels Group 1- Median (IQR)	Vitamin D Deficiency Group 2- Median (IQR)	p value
Postoperative PTH (ng/mL)	5.30 (3.5-6.6)	4.55 (1.8-7.2)	0.382
PTH month 1	16.5 (10.8-33.6)	19 (10.55-30.25)	0.970
PTH month 3	22.45 (12.3-43.6)	23.20 (13.2-32.2)	0.860
PTH month 6	25.75 (13.05-38.3)	25.95 (19.8-35.4)	0.789
Preoperative Ca (mg/dl)	9.49 (9.02-9.64)	9.35 (9.12-9.6)	0.989
Postoperative Ca (mg/dl)	7.57 (7.33-7.82)	7.66 (7.26-7.89)	0.714
Ca month 1	9.16 (8.73-9.57)	8.81 (8.25-9.48)	0.244
Ca month 3	8.9 (8.21-9.26)	8.54 (8.14-9.14)	0.340
Ca month 6	8.7 (8.12-9.25)	8.76 (8.18-9.09)	0.849
Preoperative vitamin D (pg/mL)	27.34 (24.3-40.97)	10.23 (8.38-13.52)	0.000*
Postoperative dose of Ca replacement (g)	1 (1-1)	1 (1-1)	
Postoperative dose of Calcitriol treatment (mcg)	1 (0.5-1)	0.5 (0-0.5)	

IQR: Interquartile range, PTH: Parathyroid hormone, Ca: Calcium

for the development of postoperative hypocalcemia (22), in contrast to others suggesting that preoperative vitamin D levels did not predict postoperative hypocalcemia, and therefore it was not necessary include this analysis in routine preoperative screening (16). In Turkey, more than 30% of different sample groups are reported to have vitamin D deficiency (6). Inadequate calcium absorption due to low concentrations of vitamin D results in an increase in PTH secretion, which, in turn, induces calcitriol synthesis and increases calcium absorption (23). This was also confirmed by another study reporting that vitamin D deficiency decreased intestinal calcium absorption and stimulated PTH synthesis and secretion to maintain normal calcium levels (24). Parathyroid glands need to be preserved in patients undergoing thyroidectomy or different surgery to increase PTH synthesis and secretion due to vitamin D deficiency. All these findings support the hypothesis that a normal or deficient level of vitamin D cannot prevent the development of postoperative hypocalcemia in the absence of healthy, functioning parathyroid glands.

There are many studies in the literature exploring the factors affecting transient hypocalcemia following thyroidectomy. For example, in their follow-up of 1,054 cases, Ritter et al. (21) showed that 18% of the patients developed transient hypoparathyroidism, of whom 70% recovered in two months and 5% in 12 months, but progression to permanent hypoparathyroidism was observed in 1.9%. A meta-analysis by Edafe et al. reported that the incidence of transient and permanent hypocalcemia was 27% (19%–38%) and 1% (0%–3%), respectively (9). However, only limited amount of research has been undertaken to investigate the effect of preoperative vitamin D deficiency or the normal level of this vitamin on the recovery process of this condition. Most patients with parathyroid dysfunction return to normal function within a few weeks or one month after surgery (25). We considered that the delayed recovery of parathyroid function might be due to a slow but steady increase in blood flow through neovascularization that occurs on the small surface area of the remaining parathyroid. Our study showed that preoperative vitamin D deficiency or normal level had no significant relationship with recovery time from postoperative hypocalcemia and PTH and calcium levels at postoperative months 1, 2 and 3 ($p>0.05$).

In the literature, many factors have been implicated as etiologic causes of postoperative hypocalcemia. One of the most important factors involved in postoperative calcium hemostasis is the continuation of PTH secretion, and therefore parathyroid glands should be intraoperatively preserved for the secretion of this hormone. For this reason, it is crucial for hemostasis to well define the location of parathyroid glands and preserve them during surgery. Considering that in the literature, approximately half of the glands are reported to be located in the thyroid tissue, hypocalcemia is frequently observed among thyroidectomy cases. In a meta-analysis of four studies and 1,482 patients, it was shown that parathyroid excision was significantly associated with transient hypocalcemia (26). In the current study, thyroidectomy or completion thyroidectomy was performed on many patients, and some cases required additional lymph node dissections. The risk of postoperative hypocalcemia varies depending on the type or difficulty of surgery. Recent studies have shown no significant relationship between preoperative vitamin D levels and postoperative hypocalcemia (10,21,27). In contrast, in their study with 30 patients (12 with vitamin D deficiency and 18 with normal vitamin D levels), Alkhalili et al. (22) reported that preoperative vitamin D deficiency was associated with postoperative hypocalcemia. In a systematic review and meta-analysis of observational study, Konstantina et al. reported that patients with preoperative vitamin D deficiency had an increased risk of transient hypoparathyroidism following thyroidectomy, while those with severe vitamin D deficiency had an increased risk of permanent hypoparathyroidism (28).

Most studies concerning the improvement of parathyroid function after thyroidectomy are limited in terms of sample size or duration of the postoperative follow-up period (29). The process of improvement of the parathyroid function and the variables affecting this process are still poorly understood, and therefore requires further research. More studies are necessary to clarify this multifaceted physiological mystery.

One limitation of this study is that it has a relatively small sample size. Our clinic serves a geographical area containing a significant immigrant population. Therefore, there may be problems in the effective follow-up of patients.

CONCLUSION

This study suggests that neither a normal nor a deficient level of vitamin D has a significant effect on the recovery time from hypocalcemia after thyroidectomy. Therefore, we consider that it is not necessary to measure vitamin D in routine preoperative screening or apply vitamin D replacement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University, Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (Date: 28.03.2019, Decision No: E.Kurul-E-19-2631/2631).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Monocyte and neutrophil to high density lipoprotein cholesterol ratios are elevated in patients with vitamin D deficiency

Derya Köseoğlu[1], Özden Özdemir Başer[2], Zeynep Çetin[3], Merve Çatak[4]

[1]Hitit University, Faculty of Medicine, Department of Endocrinology and Metabolism, Çorum, Turkey
[2]Yozgat State Hospital, Department of Endocrinology and Metabolism, Yozgat, Turkey
[3]Amasya University, Faculty of Medicine, Department of Endocrinology and Metabolism, Amasya, Turkey
[4]Gaziosmanpaşa University, Faculty of Medicine, Department of Endocrinology and Metabolism,Tokat, Turkey

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ABSTRACT

Aim: It is suggested that Vitamin D deficiency may lead to cardiovascular diseases. Monocyte-High density lipoprotein cholesterol (HDL) ratio (MHR) and Neutrophil-HDL ratio (NHR) are markers which may be used as cardiovascular risk factors, which are associated with inflammation. The purpose of this study is to evaluate the MHR and NHR levels in patients with Vitamin D deficiency.

Material and Method: This retrospective study included patients who were tested for Vitamin D levels in our clinic. The subjects were separated into two groups based on their Vitamin D levels and laboratory variables including MHR and NHR were compared.

Results: The subjects with serum 25 OH D level lower and higher than 20 ng/ml were compared, and MHR and NHR were detected significantly higher in subjects with Vitamin D deficiency (p:0.003 and p<0.001).

Conclusion: Our study indicates for the first time in the literature that MHR and NHR levels increase in Vitamin D deficiency. Our findings suggest that the cardiovascular risk which occurs in Vitamin D deficiency may be associated with the observed increased inflammation. It was detected that MHR and NHR ratios may be used to predict cardiovascular diseases in people with Vitamin D deficiency. Our study also showed that the increased cardiovascular risk which occurs in vitamin D deficiency may be associated with the increased inflammation.

Keywords: Atherosclerosis, vitamin D, inflammation, monocyte and neutrophil, high density lipoprotein cholesterol

INTRODUCTION

Vitamin D3 (cholecalciferol) which is the natural form of vitamin D originates from the transformation of 7-dehydrocholesterol on the skin through ultraviolet beams (1). The active form of vitamin D is 1.25-dihydroxyvitamin D (1.25 (OH) 2D) and its well known action is to ensure bone mineralization by increasing the intestinal absorption of calcium (2). 1.25 (OH) 2D acts by binding to vitamin D receptors (VDR) in many cells of the body including the cardiomyocytes, endothelium, vascular smooth muscle (3). The effects of vitamin D on the bone metabolism and musculoskeletal system are well-defined (4). The presence of VDR in many tissues led to researches regarding the effects of vitamin D on other systems apart from bone and musculoskeletal system such as cardiovascular system. Cardiovascular disease (CVD) is the leading cause of mortality and morbidity (5). Studies showed the correlation between Vitamin D deficiency and hypertension, diabetes, metabolic syndrome and immune diseases (4-7). The increased amount of evidences indicate the relationship of vitamin D deficiency with CVD risk factors and CVD mortality (4-8).

Monocytes are the most important cell type for the release of pro-inflammatory and pro-oxidant cytokines at the inflammation site, and they have a primary role in the development of atherosclerosis (9-10). Although the place of neutrophils in atherosclerosis is not clearly exhibited, it was shown that they play a role in the destabilization of atherosclerotic plaques (11). Besides,

Corresponding Author: Derya Köseoğlu, drderyaksgl@gmail.com
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it was detected that the high neutrophil ratio in the peripheral blood is associated with the increase in carotid intima media thickness which is an indicator of atherosclerosis, and it was also higher in patients with intracranial atherosclerotic plaques (12,13). High-density lipoprotein cholesterol (HDL-C) has anti-atherosclerotic activity and it has an inhibiting action on inflammatory and oxidative processes (8,14).

In formerly studies, it was shown that HDL-C inhibits the oxidation of LDL-C, and it protects the endothelial cells against the harmful effects of LDL-C (15). Low HDL-C is an independent and strong indicator for CVD (16). Due to the negative effects of low HDL-C and monocytosis, it is indicated that monocyte/HDL-C ratio (MHR) is a new prognostic indicator in cardiac diseases (17-19). While neutrophile/HDL-C ratio (NHR) is a marker which is studied less, a recent study has indicated that it is a better indicator than MHR in patients with acute myocardial infarction (20).

The relation between vitamin D deficiency and CVD was investigated in various studies, however there is no study indicating the relation of vitamin D level with MHR and NHR ratio. In this study, it is intended to show whether vitamin D level has an effect on MHR and NHR.

MATERIAL AND METHOD

The study was carried out with the permission of Yozgat Bozok University Clinical Research Ethics Committee (Date: 10.06.2020, Decision No: 2017-KAEK-189 _2020.06.10_01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The present study is a retrospective multicenter study. The study was conducted on the patients who applied to the outpatient clinics between the 1st of January 2019 and February 2020.

Fifteen thousand patients were screened and the patients who had Vitamin D levels checked were enrolled. The patients who were <18 years old; who had Type 1 or Type 2 Diabetes mellitus, prediabetes or those who were on metformin therapy; who were pregnant; who had chronic diseases such as hypertension, chronic renal disease, liver diseases, hypertension, cardiac insufficiency; who had active infection; who had hematological or immunological diseases or malignancies; who had primary hyperparathyroidism; and who were on medications for calcium and lipid metabolism and those using antihypertensive medications were excluded from the study. The demographics and anthropometric data of the patients were recorded. Body mass index (BMI) was calculated as the weight (kg)/ height(m)^2 .

Laboratory Measurements

Blood samples were obtained from patients in the morning after 12 hours of fasting, for measurement of biochemistry panel including fasting plasma glucose (FPG, 70-100 mg/dl), creatinine (Cre, normal range 0.5-1.1 mg/dl), alanine aminotransferase (ALT, normal range 8-38U/L), serum corrected calcium (Ca, normal range8.5–10.5 mg/dl), phosphorus (P, normal range2.5–4.5 mg/dl), magnesium (Mg, normal range 1.6-2.6 mg/dl), 25-hydroxyvitamin D (25 OH vit D, ng/ml), total cholesterol (normal range 0-200 mg/dl), triglyceride (normal range 0-200 mg/dl), HDL-C (normal range 45-65 mg/dl), LDL-C (normal range 0-130 mg/dl), thyroid stimulating hormone (TSH, 0.27-4.2 mU/L). Biochemical analyses were determined by standard methods. Corrected calcium was calculated as serum Ca level (mg/dl)+0.8x(4- albumin); nonHDL cholesterol was calculated as total cholesterol-HDL-C.

Samples for complete blood count (CBC) analysis were collected in EDTA anticoagulated Monovette tubes (Sarstedt, Leicester, United Kingdom). Hemoglobin level, Neutrophil count and Monocyte count were obtained from the CBC analysis. MHR and NHR ratios were determined by dividing the monocyte and neutrophil absolute levels (mm3) to HDL-C level, respectively.

Statistical Analysis

All Statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA). Normality of the distribution of the continuous variables was evaluated with Kolmogorov-Smirnov test. Continuous variables were compared with independent t-test or Mann-Whitney U test for normally and non-normally distributed data, respectively. Normally distributed data are described as mean ± standard deviation, otherwise, as median (minimum-maximum). Chi-square test was used for comparing categorical variables. The mean differences among more than two independent groups were analyzed by one-way ANOVA with Tukey post-hoc test. p values <0.05 were considered statistically significant.

RESULTS

Patients with insufficient data were excluded from the study and the statistical analysis was conducted with 554 patients. 494 of these patients were female and 60 patients were male; and the average age was 41.07±13.76 years. Patients were separated into 2 groups based on 25 OH vit D level. Patients with lower than 20 ng/ml 25 OH vit D level were determined as vitamin D deficiency (n:409) and were compared with patients who had a 25 OH vit D level of 20 and higher (n:145). The comparison of the demographics and several laboratory parameters between two groups is given in **Table 1**. According to this, it was

observed that MHR and NHR ratios were statistically significantly higher in the patients with 25 OH vit D level below 20 (p:0.003 and p<0.001, respectively).

Patients were separated into 4 groups based on the serum 25 OH vit D level, and the statistical analysis was repeated with One way ANOVA test and a statistically significant difference was observed between the groups in terms of MHR and NHR. Patients with serum 25 OH D <10 ng/ml were defined as group 1 (n:151); patients with serum 25 OH D between 10 ng/ml and 20 ng/ml were defined as group 2 (n:258), patients with serum 25 OH D between 20 ng/ml and 30 ng/ml were defined as group 3 (n:108) and patients with serum 25 OH D more than 30 mg/ml were defined as group 4 (n:37). There was a statistically significant difference in MHR between the group with serum 25 OH vit D level 20 to 30 ng/ml and the group with serum 25 OH vit D level 10 to 20 ng/ml in the post-hoc analysis (p:0.027), but no differences were detected between other groups. When considered in terms of NHR, a statistically significant increase was observed between the group with 25 OH vit D level 10 to 20 ng/ml and the group with levels 20 to 30 ng/ml and 30 ng/ml and above. In the group with 25 OH vit D level below 10, NHR was detected significantly higher compared to the group with 25 OH vit D level 20 to 30 ng/ml. One way ANOVA results are given in **Table 2**.

When a correlation analysis was performed, no correlation at a statistically significant level was detected between 25 OH vit D level and MHR or NHR.

DISCUSSION

In this study, it was detected that MHR and NHR were increased in patients with 25 OH vit D level below 20 ng/ml. No additional benefits of increasing the 25 OH vit D level above 30 could be observed according to MHR and NHR. Our study is the first study investigating the MHR and NHR levels in 25 OH vit D deficiency.

In previous studies vitamin D deficiency was named as a new cardiovascular risk factor (5). It was previously shown that the parameters such as hsCRP and carotid intima media thickness which are used as cardiovascular risk factors were increased in patients with vitamin D deficiency (8,21). It was also determined that vitamin D level is lower in diseases that constitute significant cardiovascular risk such as hypertension, metabolic syndrome and diabetes mellitus (22-24). Besides, it was observed that the cardiovascular events and cardiovascular mortality in people with vitamin D deficiency was increased compared to people with normal vitamin D levels (25,26).

Monocytes play an important role in the first-step in the development of atherosclerosis (27). Monocytes attach to the damaged vascular endothelium, proceed to subepithelial space and transform into mature macrophage. These matured macrophages catch the oxidized LDL molecules and form "foam cells", which leads to the further increase of the inflammation by releasing pro-inflammatory and pro-oxidant cytokines

Table 1. The demographic and laboratory results among the patients with serum 25 OH D levels higher and lower than 20 ng/mL

Parameter	Serum 25 OH D≥20 ng/ml (n: 145)	Serum 25 OH D<20 ng/ml (n: 409)	p
Gender (male/female)	22/123	38/371	0.061
Age (years)	45.6±14.33	39.46±13.20	<0.001
BMI (kg/m²)	28.60±5.97	30.96±7.35	<0.001
LDL-C (mg/dl)	125.69±38.84	123.71±35.14	0.592
TG (mg/dl)	118.60±57.77	125.79±71.65	0.280
T-CHOL (mg/dl)	202.86±47.54	196.90±42.76	0.190
FPG (mg/dl)	91.99±9.39	93.09±13.52	0.239
Creatinine (mg/dl)	0.69±0.14	0.64±0.13	0.001
ALT (U/L)	20.65±11.97	20.88±13.52	0.853
WBC	6941.10±1643.88	7336.66±1639.63	0.014
Hemoglobin	13.70±1.24	13.51±2.17	0.199
Monocyte/HDL-C ratio	9.80±3.70	11.03±5.20	0.003
Neutrophil/HDL-C ratio	72.42±30.08	88.04±35.75	<0.001

25 OH D: 25-hydroxyvitamin D, BMI: Body mass index, LDL-C: low-density lipoprotein cholesterol, TG:triglyceride, T-CHOL:total cholesterol, FPG: fasting plasma glucose, ALT: alanine aminotransferase; WBC:white blood cell, HDL-C: High density lipoprotein- cholesterol

Table 2. The monocyte/ high density lipoprotein cholesterol ratio and neutrophil/ high density lipoprotein cholesterol ratio among the four groups according to One way ANOVA test results

	Group 1 (n:151)	Group 2 (n:258)	Group 3 (n:108)	Group 4 (n:37)
Monocyte/HDL-C ratio*	10.56±4.44	11.30±5.59	9.74±3.44	9.98±4.48
Neutrophil/HDL-C ratio**	84.77±34.93	89.93±36.15	72.04±29.01	73.60±33.59

HDL-C: High density lipoprotein cholesterol. Patients with serum 25 OH D <10 ng/ml were defined as group 1; patients with serum 25 OH D between 10 ng/ml and 20 ng/ml were defined as group 2, patients with serum 25 OH D between 20 ng/ml and 30 ng/ml were defined as group 3 and patients with serum 25 OH D more than 30 mg/ml were defined as group 4. *p value:0.027 between group 2 and 3. ** p value<0.001 between group 2 and 3; p value:0.019 between group 1 and 3; p value:0.043 between group 2 and 4.

(28). In studies, it was shown that HDL-C inhibits the oxidation of LDL-C, and it protects the endothelial cells against the harmful effects of LDL-C, and as a result low HDL-C is an independent and strong indicator for CVD (15, 16). Due to the negative impacts of low HDL-C and monocytosis, it was shown that MHR is a new prognostic indicator for cardiac diseases (17-19,29).

There are certain numbers of neutrophils on atherosclerotic plaques, and these cause inflammatory response by accumulating on the vein wall (30). Neutrophils are the cells which are in charge in inflammatory response, and in the meantime, when they are activated, they also cause endothelial dysfunction (31,32). When the role of endothelial dysfunction in the development of atherosclerosis is considered, it is believed that neutrophil count is a parameter which may be used in the development of cardiovascular event (13). Besides, in the previous studies, leukocyte count was shown to be associated with diabetes mellitus, obesity and hypertriglyceridemia, and inflammation was shown to contribute to the development of metabolic syndrome (13,33). Such evidences indicate that neutrophils have an effect on atherosclerosis. When the role of high neutrophil and low HDL-C level in the development of atherosclerosis is taken into account, it is considered that NHR may also be used as an atherosclerosis indicator. NHR is not a commonly used parameter in atherosclerosis and cardiovascular diseases, and there are limited data in the literature about this matter. In recent studies, it was detected that NHR was a poor prognostic factor in patients who had myocardium infarction and it increased in patients with metabolic syndrome (20,34).

Although many parameters indicating cardiovascular risk in vitamin D deficiency were previously studied, the relatively new parameters MHR and NHR which may be used as cardiovascular risk indicators were not previously studied in cases of vitamin D deficiency. The purpose of this study is to investigate whether MHR and NHR increased in patients with vitamin D deficiency, and as a result of the statistical analysis, these values were determined significantly high in those with 25 OH vit D level below 20 ng/ml. In light of the data detected in our study, we consider that the increased cardiovascular risk observed in patients with vitamin D deficiency is associated with the increased inflammatory events, and that decreased HDL-C make this more evident. Serum 25 OH vit D level below 30 ng/ml is defined as vitamin D insufficiency; below 20 ng/ml as vitamin D deficiency; and below 10 is defined as severe vitamin D deficiency (35). In our study group, as there were few patients with 25 OH vit D level above 30 ng/ml, the statistical analysis was conducted according to vitamin D deficiency and those with serum 25OH vit D level below and above 20 ng/ml were compared. According to this, in patients with vitamin D deficiency, MHR and NHR were detected significantly high. Interestingly, when the serum 25 OH vit D level falls below 10 ng/ml, no significant impairment was observed in MHR and NHR. When these results are evaluated, it is possible to indicate that especially the serum 25OH vit D level above 20 ng/ml contributes to decreased cardiovascular risk. Besides, no additional harm could be shown when 25 OH vit D level falls below 10 ng/ml.

It is necessary to mention some restrictions regarding the study. Firstly, the retrospective design of the study is a restriction for our results. It would be proper to investigate whether these parameters may be used as a cardiovascular risk marker in time by a prospectively designed study. Despite the sufficient number of total patients, the number of people with 25 OH vit D level above 30 ng/ml is small, and this might have prevented us to achieve lower MHR and NHR values in higher 25 OH vit D levels, and this may be the reason for failing to obtain a significant result in the correlation analysis. Notwithstanding these restrictions, we achieved valuable data in our study and showed that MHR and NHR ratios were increased in patients with vitamin D deficiency.

CONCLUSION

As a result, our study has shown for the first time in the literature that MHR and NHR levels were increased in patients with vitamin D deficiency. It is considered that the cardiovascular risk that occurs in vitamin D deficiency may be associated with the increased inflammation and that MHR and NHR ratios may be used to predict cardiovascular diseases in vitamin D deficiency..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yozgat Bozok University Clinical Researchs Ethics Committee (Date: 10.06.2020, Decision No: 2017-KAEK-189_2020.06.10_01).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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The effect of resveratrol on toxicity caused by cisplatin in rats with experimentally created diabetes by streptozotocin

Bahattin Bulduk[1], Gökhan Oto[2], Nizamettin Günbatar[3], Mehmet Bulduk[3], Yılmaz Koçak[1], Sadi Elasan[4]

[1]Van Yüzüncü Yıl University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Van, Turkey
[2]Van Yüzüncü Yıl University, Faculty of Medicine, Department of Pharmacology and Toxicology, Van, Turkey
[3]Van Yüzüncü Yıl University, Faculty of Health Sciences, Department of Nursing, Van, Turkey
[4]Van Yüzüncü Yıl University, Faculty of Medicine, Department of Biostatistics, Van, Turkey

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ABSTRACT

Aim: In our study, the therapeutic effect of resveratrol against the toxicity of cisplatin in rats with experimental diabetes mellitus with streptozotocin was investigated.

Material and Method: 64 rats were used in the study. 8 groups were randomly formed, with 8 rats in each group. Group 1 was determined as the control group. Group 2 (STZ) was injected with 60 mg/kg streptozotocin intraperitoneally (ip) on the first day to induce diabetes. Group 3 (RES) was given 100 mg/kg of resveratrol orally every day. Group 4 (SIS), a single dose of cisplatin 7 mg/kg (ip) was administered 3 days later. Group 5 (STZ+RES), group 6 (STZ+SIS), group 7 (RES+SIS) and group 8 (STZ+SIS+RES) were determined.

Results: While there was weight gain in the control and RES groups during the experiment, the STZ and STZ + SIS groups showed a significant decrease in body weights of the rats. In the groups given streptozotocin and cisplatin together with resveratrol, there was no decrease in body weight, but a small increase was observed. In groups with increased blood glucose values with streptozotocin, these values were found to have dropped significantly with resveratrol. The TAS level has increased significantly in groups RES, STZ+RES, SIS+RES and STZ+SIS+RES according to the control group; no significant difference has been found in the other groups compared to the control group. While the AST level was significantly higher in the STZ, SIS and STZ+SIS groups compared to the control group, the ALT level was found to be significantly higher in the STZ and STZ+SIS groups compared to the control group. Creatinine was found to be significantly higher in SIS, STZ+SIS, RES+SIS and STZ+SIS+RES groups compared to the control group. The SIS group and RES+SIS and STZ+SIS+RES groups were compared, the decrease in the RES+SIS and STZ+SIS+RES groups was statistically significant. QT (ms) values increased significantly in the STZ and STZ+SIS groups compared to the control group, but there was no significant difference in the other groups. According to the control group, the heart rate per minute was found to be significantly lower in the STZ and STZ+SIS groups.

Conclusion: As a result, it was seen that the use of resveratrol would be effective in reducing the increased glucose levels in the treatment of diabetes and in the treatment of possible complications.

Keywords: Diabetes, cispilatin, resveratrol, ECG

INTRODUCTION

Diabetes is a lifelong disease that develops when the pancreas does not produce enough insulin hormone or the insulin hormone it produces cannot be used effectively. In recent years, the prevalence of diabetes mellitus has increased considerably all over the world. For this reason, many studies are carried out in this area (1).

Resveratrol is a flavonoid polyphenolic phytoalexin synthesized by plants against traumatic injury or fungal attack. Phytoalexin; It is an antibiotic produced by plants as a result of any external stress or pathogenic (fungal) attack (2).

Cisplatin is a chemotherapeutic drug used in the treatment of cancer. Unlike other antineoplastic drugs, cisplatin is a platinum derivative. It can accumulate in tissues and cause toxicity. It accumulates 5 times more in kidney tissue compared to other tissues and causes death in tubule cells (3). The most important side effect that can be encountered in the use of cisplatin is nephrotoxicity (4).

Corresponding Author: Bahattin Bulduk, bahattinbulduk@hotmail.com
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In our study, the therapeutic effect of resveratrol against the toxicity of cisplatin in rats with experimental diabetes mellitus with streptozotocin was investigated.

MATERIAL AND METHOD

The study was carried out with the permission of Van Yüzüncüyıl University Animal Experiments Local Ethics Committee (Date: 25.06.2015, Decision 2015/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Material

In the study, 64 healthy rats obtained from Yüzüncü Yıl University Faculty of Medicine Experimental Research Unit were used. Before the experiment, the rats were adapted to the ambience for 7 days. Experimental applications in the study were carried out in accordance with the maintenance conditions of laboratory animals (12 hours of light, 12 hours of darkness and 22±1°C and 60% humidity). During the experimental applications, standard commercial rat food (pellet feed) and drinking water were given to the rats ad libitum. 8 random group was created with 8 rat in each group. The rats' weights were recorded at the beginning of the study, and rats that died during the experiment and that did not have diabetes were not included in the study.

Method

1. **Group (Control):** The control group was given normal pellet rat food and drinking water throughout the experiment.
2. **Group (STZ):** To induce diabetes, rats in this group were injected with 60 mg/kg streptozotocin (intraperitoneally) on the first day. After 3 days, blood sugars were determined with blood taken from the tail.
3. **Group (RES):** The rats in this group were daily administered 100 mg/kg resveratrol by oral gavage method.
4. **Group (SIS):** A single dose of cisplatin 7 mg/kg (intraperitoneally) was administered to the rats in this group at the end of the 3rd day.
5. **Group (STZ+RES):** To induce diabetes, rats in this group were injected with 60 mg/kg streptozotocin (intraperitoneally) on the first day.100 mg/kg resveratrol was given daily by oral gavage method
6. **Group (STZ+SIS):** To induce diabetes, rats in this group were injected with 60 mg/kg streptozotocin (intraperitoneally) on the first day. Then, a single dose of cisplatin 7 mg/kg (intraperitoneally) was administered.
7. **Group (RES+SIS):** The rats in this group were daily administered 100 mg/kg resveratrol by oral gavage method.. Then, at the end of the 3rd day, a single dose of cisplatin 7 mg/kg (intraperitoneally) was administered.
8. **Group (STZ+SIS+RES):** To induce diabetes, rats in this group were injected with 60 mg/kg streptozotocin (intraperitoneally) on the first day. The rats in this group were given 100 mg/kg resveratrol daily by oral gavage method. A single dose of cisplatin 7 mg/kg (intraperitoneally) was administered 3 days later.

Streptozotocin was suspended in sodium citrate buffer (pH: 4.5) and resveratrol was suspended in dimethylsulfoxide and administered to experimental animals. In the STZ treated groups, blood glucose levels were determined 3 days later by blood taken from the tail. Rats with blood glucose of 250 mg/dl and above were accepted as diabetes (5,6). The study took 14 days.

Electrocardiography (ECG) Shot

After the experimental applications, the rats were anesthetized with 50 (mg/kg) ketamine (ip). The rats were placed on the table in the right lateral position for ECG recording. The hairs on the upper parts of the elbow and knee joints of the rats were removed and cleaned with alcohol. Electrode gel was applied to the upper part of the elbow and knee joint to facilitate current flow. Then, crocodile-mouth electrodes were placed over the elbow joint in the forelimbs and over the knee joint in the hind limbs. The ECG device was adjusted to be 1 mV=10 mm and printing speed 50 mm/sec (7).

Taking Blood Samples

After ECG recordings, the rats were placed on the table in the dorso-ventral position. The right hand was grasped by the neck of the rat, and the thumb and index fingers and front legs were held tightly and stretched. The hairs on the thorax were shaved, the skin was wiped with alcohol, the heartbeat point was determined with a finger, the cannula was inserted vertically at a distance of 2-3 mm from the left edge of the sternum in the 2nd and 3rd intercostal space, and the blood was taken with an injector. The collected blood was transferred to the tubes and centrifuged and serum and plasma were collected.

Statistical Analysis

Descriptive statistics for continuous variables in our study; Expressed as Median, Mean, Standard Deviation, Minimum and Maximum values. The Kruskal Wallis test was used to compare group means in terms of continuous variables. Duncan test was used to identify different groups. The statistical significance level was taken as 5% in the calculations and the SPSS (ver.23) statistical package program was used for the calculations.

RESULTS

In this study, which was conducted to investigate the therapeutic effects of resveratrol in rats with experimental diabetes, the experimental animals used during the 14-day trial period were weighed on the 1st and 14th days. While weight gain was found in the control and RES groups during the 14 day experiment, it was determined that there was a significant decrease in the body weights of the rats in the STZ and STZ+SIS applied groups. In the groups given resveratrol together with STZ, there was no decrease in body weights, but a small increase was observed.

The blood values and ECG findings of the experimental animals are given in **Figure 1**. While the TAS level increased significantly in the RES, STZ+RES, SIS+RES and STZ+SIS+RES groups compared to the control group, no significant difference was found in the other groups compared to the control group. Considering the TOS values in the study, no statistically significant difference was found between the group averages. However, TOS values in all STZ applied groups increased compared to the values in the control group. Considering only the STZ applied group and the STZ+RES group, a decrease was observed in the STZ+RES group, although not statistically significant. While the AST level was significantly higher in the STZ, SIS and STZ+SIS groups compared to the control group, the difference was insignificant in all other groups compared to the control group. According to the ALT level control group, the difference between STZ and STZ+SIS groups was found to be meaningless, compared to control in all other groups. Creatinine increased significantly in SIS, STZ+SIS, RES+SIS and STZ+SIS+RES groups compared to the control group. When only the SIS group and the RES+SIS and STZ+SIS+RES groups were compared, the decrease in the RES+SIS and STZ+SIS+RES groups was statistically significant. Considering the glucose values, the increase in the STZ and STZ+SIS groups was found to be significant compared to the other groups.

QT (ms) values increased significantly in the STZ and STZ+SIS groups compared to the control group, but there was no significant difference in the other groups. Compared to the control group, the heart rate per minute was found to be significantly lower in the STZ and STZ+SIS groups. While cisplatin alone did not cause a decrease, a significant decrease was observed when administered with STZ no significant difference was found in the other groups.

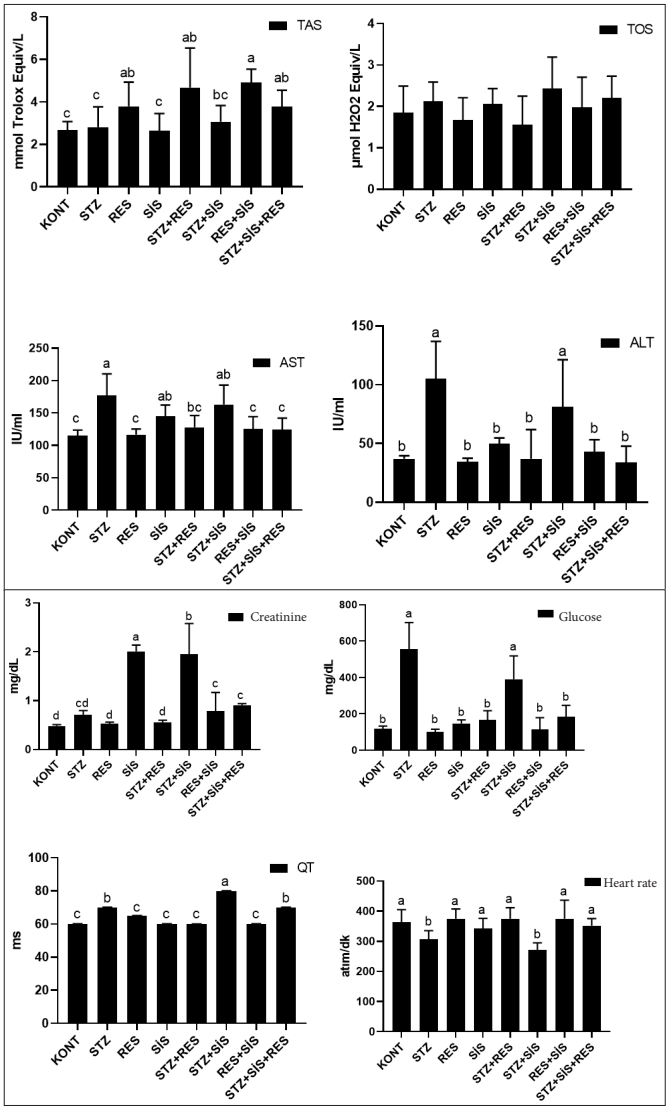

Figure 1. The results of TAS, TOS, AST, ALT, Creatinine and glucose analysis in blood samples taken from rats and QT and heart rate values according to groups in terms of ECG values.

DISCUSSION

It is estimated that 4 out of every 100 people in the world will have diabetes in the next 10 years due to the unhealthy diet, sedentary life and the resulting excess weight brought about by city life in recent years. Diabetes mellitus, which is caused by a combination of hereditary and environmental factors and results in an increase in blood glucose level, is a lifelong metabolic disease that causes carbohydrate, fat and protein metabolism disorders that occur as a result of the deficiency or ineffectiveness of the insulin hormone (8). Diabetes is known to damage various organs and tissues. The most important complications of diabetes are retinopathy, neuropathy and nephropathy (9). In the later stages of diabetes, glomerular and renal vascular lesions as well as acute and chronic pyelonephritis can be observed (10). Diabetes is a risk factor for heart failure. It can reveal ischemia and arrhythmias in the heart (11). The very common streptozotocin (STZ) was used to create a diabetes model in experimental animals (12). In the study of Green et al. (13), a single dose of 60 mg/kg (ip) STZ was administered in our study, since it was reported that a single dose of 40-60 mg/kg STZ in rats would be sufficient to create a diabetes model. As it is known, nephropathy and cardiopathy

are chronic complications of diabetes. Our work was concluded in a short period of 14 days. It was thought in our study the toxic effect of cisplatin could be benefited from in order to see the long-term damage of diabetes. The effect of resveratrol against the toxicity of both STZ and cisplatin was determined. In this study, in accordance with the literature, it was found that body weight decreased statistically significantly in the groups with diabetes (STZ, STZ+SIS) (14,15). Resveratrol administration is known to slow down weight loss caused by diabetes. It is thought that body weights of rats with diabetes decreased as a result of polyuria, increased protein and lipid breakdown. It was determined that body weights that decreased with diabetes in rats did not decrease in resveratrol given treatment groups (STZ+RES and STZ+SIS+RES). In our study, the fact that RES application prevented weight loss in diabetic rats is in parallel with other studies (16,17).

In the diabetic groups who received RES for treatment, the decreased glucose level was statistically significant. When the blood glucose level in the STZ+RES group at the beginning of the study was compared with the blood glucose level at the end of the study, a significant decrease was detected. The therapeutic effect of resveratrol has also been shown in similar studies (18,19). Nihei et al., in 2001 in their study in rats caused the phosphorylation of GLUT4, one of the glucose transporters, by affecting the insulin receptors of resveratrol; reported that blood glucose level decreased by increasing glucose uptake into the cell (20). In another study, they stated that resveratrol decreased the plasma glucose level in diabetic rats (21). In our study, we think that resveratrol normalizes the high blood glucose level by affecting the transport systems involved in glucose transport. As a result of certain reactions in the body, harmful wastes called oxidants occur. The biological damage caused by these harmful wastes in the organism is known as oxidative stress. There are endogenous and exogenous antioxidant molecules that prevent the oxidative effects of free radicals, that is, oxidative stress in the organism. They protect cells from the damaging effects of oxidant agents. It is necessary to measure total oxidant (TOS) to determine the amount of oxidant in the body, and total antioxidant (TAS) measurement to determine the amount of antioxidant (22). In our study, TAS and TOS levels were measured in the sera obtained. While the TAS level was found to be significantly higher in the RES, STZ+RES, SIS+RES and STZ+SIS+RES groups, that is, in all groups given resveratrol, compared to the control group, no significant difference was found in the other groups compared to the control group. In a study by Rodrigo and Bosco in 2006, they reported that resveratrol has a protective effect against kidney damage due to its free radical scavenger and enzyme regulatory effect (23). In another study, it was determined that resveratrol has a protective effect against oxidative damage caused by ethanol in different organs (24). Similar studies support the antioxidant property of resveratrol in our study (25,26,27). In our study, it was found that resveratrol increased TAS levels. Resveratrol is thought to protect the body against oxidative stress by eliminating the harmful effects of free radicals. Resveratrol is known to be a phytoalexin. Resveratrol is known to increase the resistance of vessels against oxidative stress by protecting endothelial cells in apoptotic cell death caused by hydrogen peroxide. It is thought that resveratrol is a natural antioxidant, inhibiting the superoxide radical that occurs in mitochondria, reducing the oxidative chain complex and inhibiting lipid peroxidation (28,29,30). It has been observed that the antioxidant aspect of resveratrol is also effective in conditions that cause great biological damage to the organism, such as diabetes and cisplatin. Considering the TOS values in the study, no statistically significant difference was found between the group averages. However, TOS values in the STZ and cisplatin applied groups were higher than the values in the control group. When only the STZ applied group and the STZ + RES group were examined, it was observed that although it was not statistically significant in the STZ + RES group, a decrease was observed, and at the same time, a result closer to the control group. The higher TOS value in the STZ+SIS group compared to the STZ+SIS+RES group is thought to protect the body against oxidant damage by resveratrol. Resveratrol is thought to be a powerful antioxidant by stimulating antioxidant enzymes, and stabilizes radical derivatives due to its hydroxylated structure and prevents oxidative damage (31).

Aminotransferases (AST and ALT) are particularly known as markers of liver damage. But they are also found in the heart and skeletal muscle, as well as in the brain, pancreas, kidney, lung, and erythrocytes. While the AST level was significantly higher in the STZ, SIS and STZ+SIS groups compared to the control group, the difference was insignificant in all other groups compared to the control group. While ALT level increased significantly in the STZ and STZ+SIS groups compared to the control group, the difference was insignificant in all other groups compared to the control group. It was determined that AST and ALT levels increased significantly in the groups given STZ and SIS, while these rates decreased in the groups given RES. This showed us that resveratrol has a preventive effect on the toxic effects caused by STZ and SIS. In similar studies with resveratrol, the same effect was found (32-34). In a study by Juan et al. (35) in 2002,

Sprague-Dawley administered resveratrol orally 20 mg/kg per day for about a month in rats. At the end of the study, they reported that there was no significant change in ALT and AST enzyme levels. Ghosh et al. (36) in their study in 2014, reported that 60 mg/kg STZ administration increased AST and ALT values, which are markers of hepatic dysfunction. They have proven that STZ causes liver damage. Yousef et al. (37) in their study in rats in 2009, showed that cisplatin caused liver damage and increased liver enzymes. In our study, we think that the administration of STZ and SIS caused liver damage, therefore the transport functions were impaired, membrane permeability changed, thus the levels of enzymes changed.

In this study, we found that resveratrol alone did not cause a change in AST and ALT values. The therapeutic effect of resveratrol was thought to be due to its regulation of the formation of inflammatory mediators by providing the oxidant and antioxidant balance. Creatinine increased significantly in SIS, STZ+SIS, RES+SIS and STZ+SIS+RES groups compared to the control group. In 2011, Alhaider et al. (38) reported that there was a significant increase in serum creatinine levels after 8 weeks in rats that they created a diabetes model with STZ. We have seen this situation in our own study. When only the SIS group and the RES+SIS and STZ+SIS+RES groups were compared, the decrease in the RES+SIS and STZ+SIS+RES groups was statistically significant. After cisplatin use, increased creatinine level, decreased clearance and electrolyte imbalance are indicators of nephrotoxicity (3,39). It shows that resveratrol is effective against nephrotoxicity caused by electrolyte imbalance by regulating creatinine level.

ECG, which is a frequently used and important diagnostic method in the evaluation of heart diseases, is the process of recording the action currents that occur during the operation of the heart and are distributed over the body surface (40). The QT interval is the total time indicative of the depolarization and repolarization of the ventricles. It is determined by measuring the portion from the beginning of the QRS complex to the end of the T wave. Long QT syndrome with syncope and sudden cardiac death is a risk factor for fatal ventricular arrhythmias. Prolongation of the QT interval may cause "torsade de pointes" type ventricular arrhythmias in bradycardia and electrolyte imbalances (hypopotashemia, hypomagnesemia) (41). The prolongation of the QT interval is usually due to the prolongation in the repolarization section of the ventricles (42). In studies conducted in rats, long QT values have been reported as a sign of hypokalemia and myocardial infarction (43,44). During this study, rats were anesthetized with 50 (mg/kg) ketamine (ip). The averages of QT values in this study show similarities with the studies performed in rats under anesthesia (45,46). In our study, QT (ms) values increased significantly in the STZ and STZ+SIS groups compared to the control group, but no significant difference was found in the other groups. Resveratrol corrected QT prolongation caused by streptozotocin and cisplatin. Li-Man Hung et al. (2) reported that resveratrol has a therapeutic effect in arrhythmias after ischemia. In addition, the similarity of QT values in the group given only resveratrol compared to the control group may also be an indication that resveratrol does not cause any arrhythmia. Hashemzaei et al. (47) reported that resveratrol alone had no effect on ECG parameters and they did not find a significant result compared to the control group, confirming this information. In our study, it is thought that resveratrol has cardioprotective and arrhythmia regulating effectsThis can be explained by the fact that resveratrol reduces the amount of free radicals formed during cardiotoxicity. The results we found are similar to the literature (2,48-51).

Electrocardiogram R-R interval gives information about the heart rate. The values in the studies on heart rate in rats under anesthesia show parallelism with the values in our study (52,53). In the statistical analysis, the difference of the R-R interval between the group averages in the study was found to be significant. It was determined that the R-R (sec) interval was prolonged in the STZ and STZ+SIS groups compared to the control group. Compared to the control group, the heart rate per minute was found to be significantly lower in the STZ and STZ+SIS groups. While cisplatin alone did not cause a decrease, a significant decrease was observed when administered with STZ. Vilar-Pereira et al. (54) reported in their study that resveratrol reduces prolonged PR and QTc intervals, increases heart rates and improves cardiac output. In our study, we found that resveratrol increased the low heart rate caused by STZ and SIS application and shortened the prolonged R-R intervals, that is, brought them closer to the control group values. In a study on resveratrol, it was reported that it increased the amount of adenosine in the heart tissue (55). Adenosine is known as a cardiac protector with its effects such as normalization of cardiac functions and suppression of arrhythmias. The rhythm-regulating effect of resveratrol can be explained by increasing the amount of adenosine. In the literature review, no information was given about how it would affect the heart rate in rats given administered streptozotocin and cisplatin. More studies on the subject need to be done.

CONCLUSION

The therapeutic effect of resveratrol on STZ and cisplatin-induced biological damage was examined.It was determined that resveratrol played a regulatory role on biochemical parameters and cardiac arrhythmias.As a result; we concluded that resveratrol prevents diabetes-induced weight loss, lowers elevated blood sugar levels, has antioxidant properties and a therapeutic effect on liver damage, lowers prolonged QT times, and regulates heart rate.We think that the use of resveratrol will be beneficial in the treatment of diabetes and tissue damage caused by cisplatin.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Van Yüzüncüyıl University Animal Experiments Local Ethics Committee (Date: 25.06.2015, Decision 2015/08).

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Primary bone tumors and tumor-like lesions of the wrist: a single-center experience

Ömer Sofulu
Marmara University, Faculty of Medicine, Department of Orthopaedic Surgery and Traumatology, İstanbul, Turkey

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ABSTRACT

Aim: The incidence of primary bone tumors of the wrist is increasing. The aim of this study was to examine the characteristics, treatment protocols, complication rates, and functional outcomes of bone tumors of the wrist treated in a tertiary orthopedic oncology center.

Material and Method: We retrospectively analyzed 93 patients with bone tumors located in the wrist (63 distal radius, 23 distal ulna, 7 carpal bone) who were operated on between 2005 and 2020. Demographic information was recorded. Functional outcomes were evaluated with the Musculoskeletal Tumor Society System (MSTS) scoring system.

Results: There were 57 male and 36 female patients. The average follow-up period was 32 months (range 16-163). There were 82 benign and 11 malignant lesions. Distal radius was the most common site of involvement. The most common type of benign tumor in the distal radius and distal ulna was the giant cell tumor (GCT; 26 and 10 patients, respectively). Among the malignant tumors in the distal radius, 5 were Ewing sarcoma, and 2 were osteosarcoma. All patients with malignant lesions underwent wide surgical resection and free vascularized fibular graft (FVFG) reconstruction. Of the malignant tumors in the distal ulna, 3 were Ewing sarcoma, and 1 was osteosarcoma. These were treated with wide resection and FVFG reconstruction (n=3) and wide resection and fibular strut graft (n=1). The rarest site for tumors in the wrist was the carpal bones. Carpal bone lesions included scaphoid (n=5) and lunate (n=2) tumors. In all of these patients, pathological examination indicated intraosseous ganglion cysts. The average MSTS score of all patients was 27 (range 24-30). Of the 36 patients with GCT, 4 (11%) developed local recurrence. One patient with Ewing sarcoma developed local recurrence and underwent secondary amputation. Distant lung metastasis was observed in 5 of 8 patients with Ewing sarcoma.

Conclusion: Our study confirmed that bone tumors in the wrist are rare. Most benign tumors can be treated with curettage and cement augmentation. For malignant tumors, it is possible to restore function with FVFG.

Keywords: Wrist, primary bone tumor, benign, malignant, incidence

INTRODUCTION

The wrist joint consists of the distal radius, distal ulna, and eight carpal bones. In addition to this complex bone structure, the wrist is also comprised of tendons and muscles on the volar and dorsal sides. This remains a challenge for orthopedic oncologists. Bone tumors are rarely found in hand and wrist compared to the other parts of the body (1). Although there are large patients series concerning bone tumors in the elbow and shoulder joint, to the best of our knowledge, studies on wrist tumors are limited to single-center experiences.

Several surgical procedures have been reported for primary bone tumors of the distal radius and distal ulna (2-5). Surgical methods for the treatment of carpal bones have been presented as case reports with limited numbers of patients (6,7). Benign tumors are often treated with curettage, grafting, cement augmentation, or marginal excision (5,8). The literature demonstrates the success of wide surgical resection with biological reconstruction in the treatment of malignant bone tumors (9,10). Wrist bone tumors are becoming increasingly common, and advanced imaging methods allow early diagnosis and treatment (9). Therefore, it is important to understand the clinical, oncological and functional outcomes of wrist tumors to improve patient survival and function.

The aim of this study was to evaluate the incidence of wrist tumors, surgical methods, associated complication rates, and functional outcomes among patients operated for wrist tumors in our clinic.

Corresponding Author: Ömer Sofulu, omersofulu@gmail.com
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MATERIAL AND METHOD

The study was carried out with the permission of Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date: 03.01.2020, Decision No: 09.2019.1033). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We retrospectively reviewed the files of 105 patients who were surgically treated for wrist tumors between 2005 and 2020. We excluded eight patients with metastatic lesions and four patients due to irregular follow-up. Of the remaining 93 patients, 63 had distal radius tumors, 23 distal ulna tumors, and seven carpal bone tumors.

Patient data were obtained from hospital archives including, age, sex, the affected side, complaints at admission, tumor type, size and stage of the tumor. The Enneking surgical staging system was used for tumor staging (11). Tumor size was determined by the same musculoskeletal radiologist based on MRI and CT studies. All histopathological examinations were performed by the same pathologist. Surgical treatment methods and related complications were reviewed for benign and malignant tumors. Final Musculoskeletal Tumor Society System (MSTS) scores were used to assess functional outcomes.

The routine chemotherapy treatment protocol was IE-VAC (ifosfamide, epirubicin, vincristine, adriamycin, cisplatin) for Ewing sarcoma patients. On the other hand, osteosarcoma patients received preoperative (neoadjuvant) and postoperative (adjuvant) chemotherapy, including epirubicin, cisplatin, ifosfamide at the same center.

All patients were called in for weekly follow-up visits for the first month after surgery and then every three months for the first year. Subsequently, patients with benign tumors were invited for follow-up visits every year, and malignant tumors, every six months. For the patients with malignant tumors, six-month follow-up visits included abdominal and thoracic computed tomography (CT) and positron emission tomography (PET) images.

Data were analyzed using SPSS v.21 (IBM Corporation, Armonk, NY, USA). The results were reported as descriptive statistics, namely mean, median, standard deviation, minimum and maximum, and percentage.

RESULTS

The study included 57 male and 36 female patients. The average follow-up period of the study was 32 months (range 16-163). There were 63 distal radius tumors, 23 distal ulna tumors, and seven carpal bone tumors. There were 82 benign and 11 malignant lesions. The lesions involved the right wrist in 65 patients and the left wrist in 28 patients (**Table 1**).

Table 1. Summary data of patients characteristics and functional outcomes

	Distal radius n=63	Distal Ulna n=23	Carpal bones n=7	Total n=93
Male/female	46/17	7/16	4/3	57/36
Benign/malign	56/7	19/4	7/0	82/11
Right/left	49/14	14/9	2/5	65/28
Age (year) (mean±SD)	22.9±14.01	32.27±16.9	39.2±11.9	31.3±14.3
Tumor size (mm) (mean±SD)	41±20.87	29.8±19.9	7±4	25.9±14.9
Tumor Stage				
Stage 1	0	0	7	7
Stage 2	8	9	0	17
Stage 3	48	10	0	58
Stage IIA	5	3	0	8
Stage IIB	2	1	0	3
Complaint				
Pain+swelling	52	21	5	78
Deformity	4	1	0	5
Incidental	0	3	2	5
Pathological fx at diagnosis	0	1	0	1
Tumor type				
Benign				
GCT	26	10	0	36
ABC	15	4	0	19
UBC	4	0	0	4
Osteoblastoma	3	0	0	3
Osteochondroma	3	3	0	6
Enchondroma	3	0	0	3
Osteoid osteoma	1	1	0	2
Desmoid tumor	1	0	0	1
IOGC	0	1	7	8
Malign				
Osteosarcoma	2	1	0	3
Ewing sarcoma	5	3	0	8
MSTS Last F-U mean (range)	28 (25-30)	27 (24-29)	28 (27-29)	28 (24-30)

Abbreviations: fx: fracture, GCT: giant cell tumor, ABC: aneurysmal bone cyst, UBC: unicameral bone cyst, IOGC: intraosseous ganglion cyst, MSTS: Musculoskeletal Tumor Society System, F-U: follow-up

Distal Radius (n=63)

Distal radius was the most common site of involvement. The mean age of patients with distal radius tumors was 23±14 years. Among these patients, 52 presented with pain and swelling in the wrist, and four had accompanying deformities. The mean tumor size was 41±20.87 mm. Enneking stage 3 was the most common disease stage (n=48). The most common benign tumor in the distal radius was giant cell tumors (GCT, n=26), followed by aneurysmal bone cysts (ABC, n=15) (**Figure 1**). Benign distal radius tumors (n=56) were treated with curettage and cementing (n=45), curettage and grafting (n=5), and marginal excision (n=6) (**Table 2**). Malignant tumors of the distal radius (n=7) included Ewing sarcoma (n=5) and osteosarcoma (n=2), all of which were treated with wide surgical resection and free vascularized fibular graft (FVFG) reconstruction (**Figure 2**). The postoperative splint was applied to all malignant radius tumors and 50 out of 56 benign tumors. Osteosynthesis with plate screw or percutaneous pinning was performed in all malignant patients and 32 benign patients. One patient developed a superficial infection and was treated with oral antibiotics. Three patients with GCTs in the distal radius developed local recurrence at an average of 76 months (range 54 to 93) after surgery (**Table 3**). These patients were treated with re-curettage and cementing. Four patients with Ewing sarcoma developed distant lung metastasis. They were treated with metastasectomy followed by chemotherapy. The mean final MSTS score of the patients with distal radius tumors was 28 (range 25-30).

Table 2. Surgical treatment types

	Distal radius	Distal Ulna	Carpal bones	Total
Benign				
Marginal resection	6	5	1	12
Curettage+graft	5	7	6	18
Curettage+PMMA	45	7	0	52
Malign				
Wide resection+FVFG	7	3	0	10
Wide resection+strut fibular graft	0	1	0	1

Abbreviations: PMMA: polymethyl methacrylate, FVFG: free vascularized fibular graft

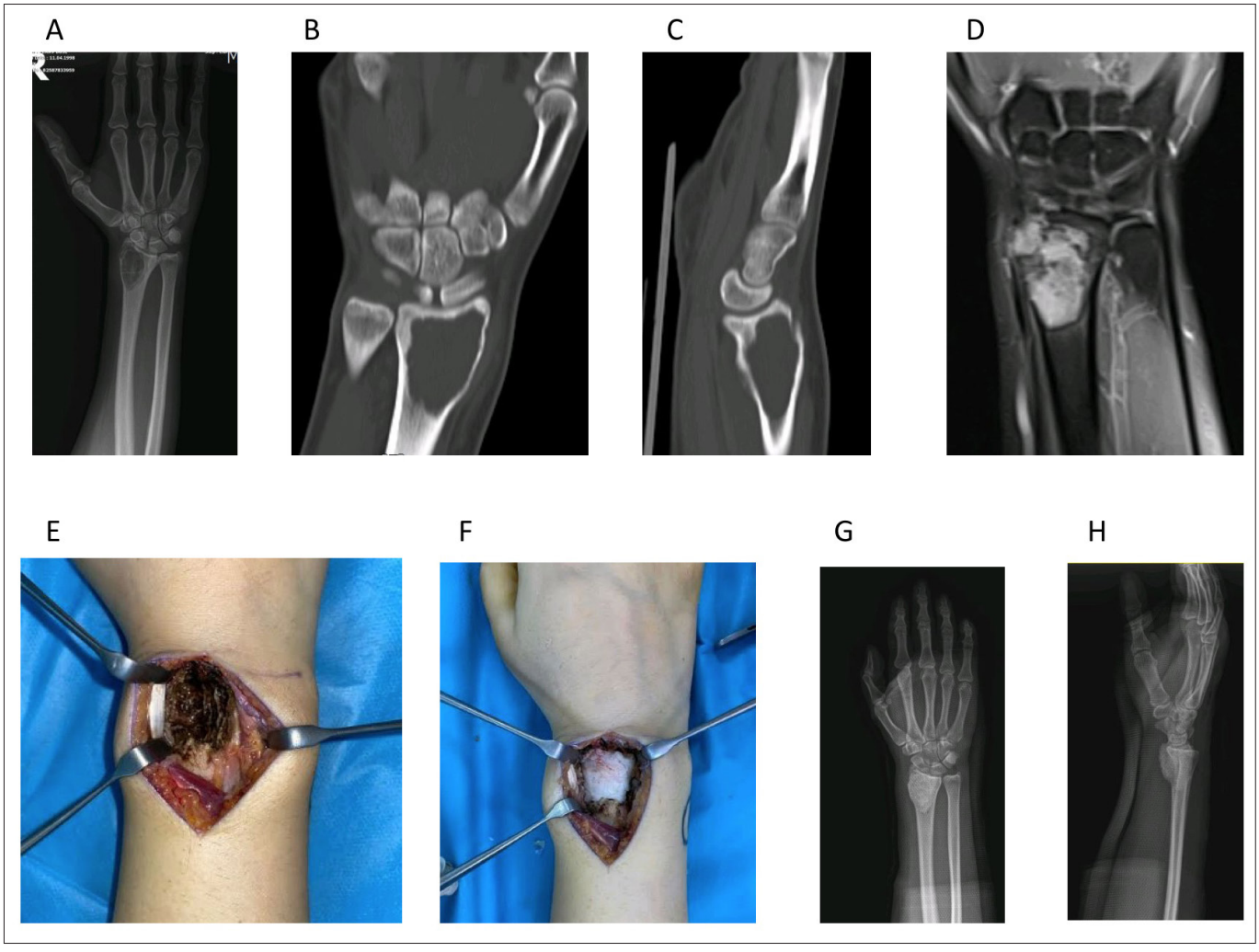

Figure 1. A 24-year-old female with distal radius giant cell tumor: a) preoperative plain radiograph, b,c) preoperative computarized tomography d) preoperative magnetic resonance image, e,f) the patient underwent curettage followed by cementation, g,h) postoperative plain radiograph.

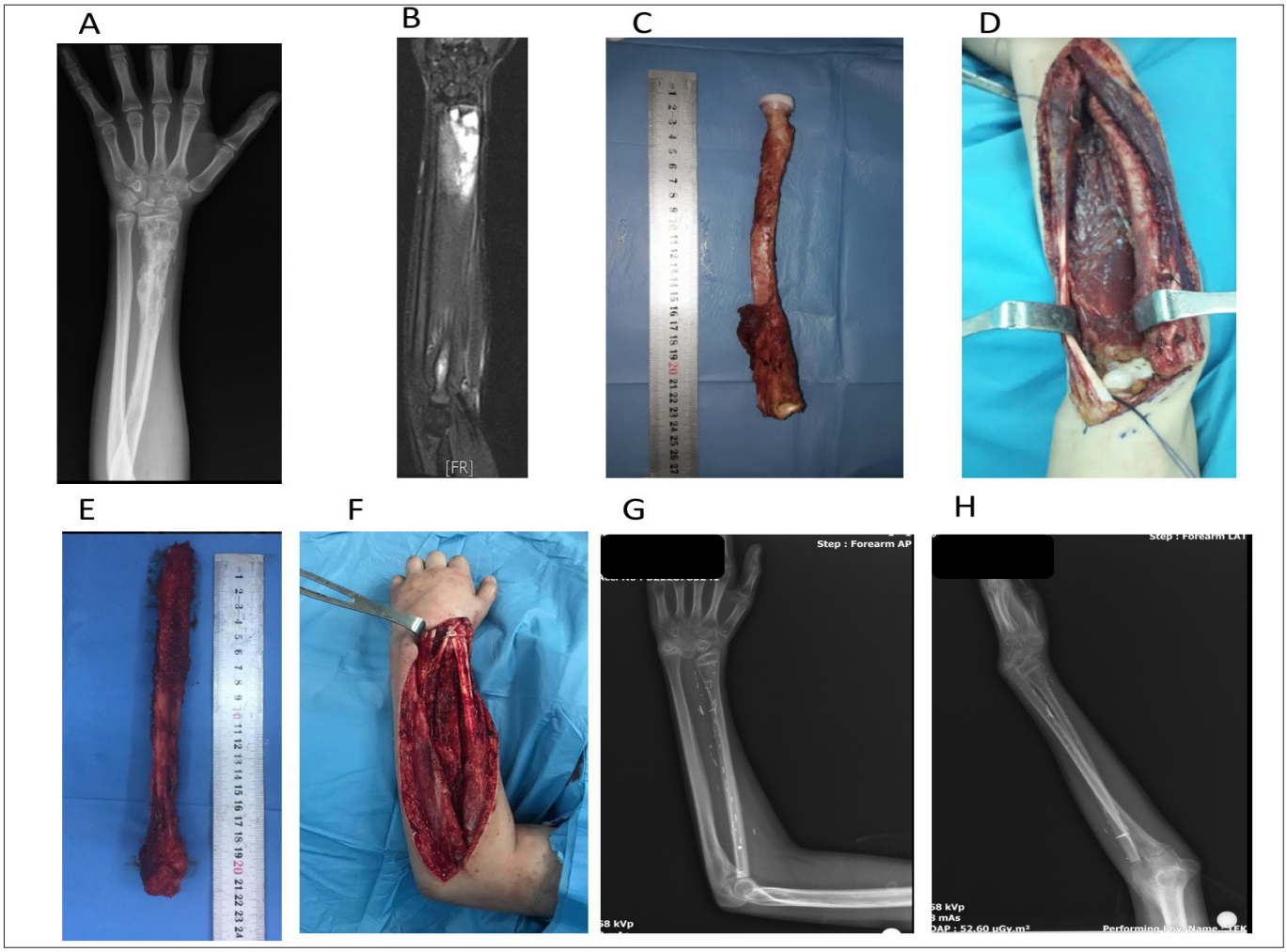

Figure 2. A 14-year-old female radius distal Ewing sarcoma, a) preoperative plain radiograph, b) preoperative magnetic resonance image, c,d,e,f) the patient had wide resection and biological reconstruction with osteoarticular vascularized fibular head graft, g,h) postoperative plain radiograph.

Table 3. Complication after surgical treatment

	Distal radius	Distal Ulna	Carpal bones	Total
Superficial infetion	1	1	0	2
Wound dehissance	0	1	0	1
Pathological fx. during F-U	0	1	0	1
Deformity during F-U	0	1	0	1
Local recurrence	3 GCT	1 GCT/1Ews	0	5
Distant metastasis	4Ews	1Ews	0	5

Abbreviations: F-U: follow-up, fx: fracture, GCT: giant cell tumor, Ews: Ewing sarcoma

Distal Ulna (n=23)

The mean age of patients with distal ulna tumors was 32±17 years. Twenty-one patients presented with pain and swelling, and one patient with wrist deformity. One patient had a pathological fracture at the time of admission. Three lesions were incidentally identified. The mean tumor size was 29.8±19.9 mm. Enneking stage 3 was the most common disease stage. The most common benign tumor in the distal ulna was giant cell tumors (GCT, n=10), followed by aneurysmal bone cysts (ABC, n=4). Benign distal ulna tumors (n=19) were treated with curettage and cementing (n=7), curettage and grafting (n=7), and marginal excision (n=5) (**Figure 3**). Malignant tumors of the distal ulna (n=4) included Ewing sarcoma (n=3) and osteosarcoma (n=1) and were treated with wide resection and FVFG (n=3) and wide resection followed by strut fibular grafting (n=1). The postoperative splint was applied to all malignant ulna tumors and 16 out of 19 benign tumors. Osteosynthesis with plate screw or percutaneous pinning was performed in all malignant patients and 12 benign patients. One patient developed a superficial infection and was treated with oral antibiotics. In follow-up, One patient with distal Ewing sarcoma developed a pathological fracture, and one patient developed a deformity. These patients were treated with reduction followed by osteosynthesis with plate and screws. Local recurrence was detected in one patient with a giant cell tumor and one patient with Ewing sarcoma. GCT recurrence was treated with re-curettage and cementing. The recurrent Ewing sarcoma was treated with amputation. One patient with Ewing sarcoma developed lung metastasis at 42 months and underwent metastasectomy followed by chemotherapy. The mean final MSTS score of the patients with distal ulna tumors was 27 (range 24-30).

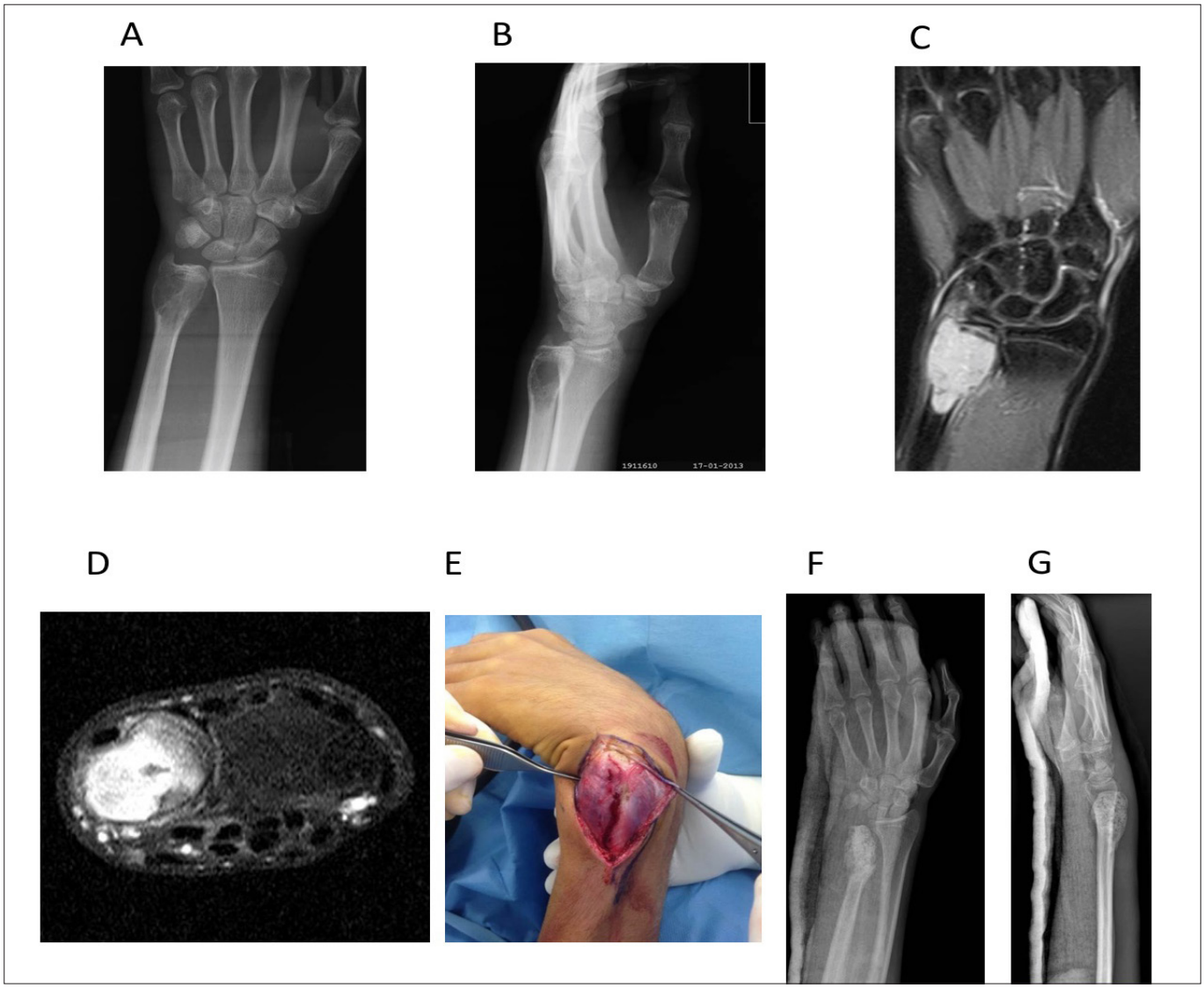

Figure 3. A 28-year-old male with distal ulna aneurysmal bone cyst a,b) preoperative plain radiograph, c,d) preoperative magnetic resonance image, e) the patient underwent curettage followed by grafting, f,g) postoperative plain radiograph.

Carpal Bones (n=7)

Wrist tumors were the rarest in carpal bones (n=7). The mean age in this subgroup was 39±12 years. The mean tumor size was 7±4 mm. Carpal bone lesions included scaphoid (n=5) and lunate (n=2) tumors. In all of these patients, pathological examination indicated intraosseous ganglion cysts. Five patients initially presented with pain and swelling, and two patients were incidentally identified. The patients were treated with curettage and grafting (n=6) and marginal excision (n=1). The mean final MSTS score of these patients was 28 (range 27-29). The postoperative splint was applied to all carpal benign tumors.

DISCUSSION

Bone tumors of the wrist are rare. Most benign tumors can be treated with curettage and cementing. The wide resection of malignant tumors remains a challenge for orthopedic oncologists due to the anatomical complexity of the hand and wrist region. This study reviewed the clinical, oncological, and functional outcomes of patients who were treated in a tertiary orthopedic oncology clinic for wrist bone tumors. In this study, the most common type of benign tumor was GCT, followed by ABC. The most common malignant tumor was Ewing sarcoma, and biological reconstruction yielded favorable outcomes in these patients. Locally recurrent GCTs were treated with re-operation, namely curettage and cement augmentation. One patient with Ewing sarcoma who developed local recurrence underwent secondary amputation. Two patients developed superficial infections and were treated with oral antibiotics.

The Rizzoli case archives indicate that wrist tumors accounted for only 400 (2.1%) of the 18948 primary bone tumors (12). The literature presents case report series about the distal radius, distal ulna, and carpal bones (4-8). This study included 93 patients who were operated on for wrist tumors in a tertiary orthopedic oncology center over a 15-year period, indicating that the wrist region is a rare site for bone tumors.

In our study, the most common tumor was GCT, and the lesions were most often localized in the distal radius. Different methods were described for the treatment of giant cell tumors. The most widely accepted treatment method is curettage, followed by cement augmentation (5). In our study, curettage with cement augmentation yielded favorable outcomes in patients with GCTs, in accordance with the literature. Crowe et al. (13) reported that 4 (36%) out of 11 ABCs of the distal upper extremity were localized in the wrist. In our study, ABCs comprised 20% of all wrist tumors. In our study, ABCs were mostly treated with curettage followed by grafting with success. None of these patients developed deformities or osteoarthritis in follow-up.

The literature reports that 84-100% of all distal radius tumors are Enneking stage 3 (14,15). In our study, this number was 85.7%, consistently with the literature. 71% of the malignant lesions were stage IIA at the time of admission. In our patient series, there were no patients with distant metastases (stage IIIB) at the time of diagnosis. We attribute this finding to rapid admission to the hospital after swelling or pain in the wrist.

When treating malignant tumors of the distal radius, we performed wide resection of the tumor, followed by autografting with a vascularized fibular head graft which is anatomically compatible with the distal radius. The literature reports outcomes for biological reconstruction with a fibular head graft (16). Previous studies have reported good functional outcomes for the hand due to the anatomical compatibility of the fibular head with the scapholunate joint (16,17). In the current study, we obtained an average MSTS score of 26 (range 25-27) using vascularized fibular head grafts. Further larger studies with longer follow-up can more reliably demonstrate long-term outcomes.

Primary bone tumors of the ulna are quite rare (18). Rizzoli case archives indicate that only 0.9% of all primary bone tumors are localized in the ulna (12). In their series of 2000 patients, Exner et al. (19) reported ulnar involvement in 24 cases. Aycan et al. (18) showed that 8 of 23 primary tumors of the ulna were localized in the distal ulna. Consistently with the literature, we also observed that tumors in the distal ulna (n=23) are rare. Although the primary reason of admission was pain and swelling for lesions in the distal ulna, one patient presented with a pathological fracture. In their series of primary tumors of the ulna, Aycan et al. (18) reported that the most common types of benign lesions were osteochondroma and ABC, and the most common type of malignant lesion was osteosarcoma. In this study, the most common benign tumors involving the distal ulna were GCT and ABC, and the most common malignant lesion was Ewing sarcoma. Malignant tumors of the distal ulna were treated with wide resection and FVFG (n=3), and strut fibular grafting (n=1). The mean final MSTS score was 27 (range 24-29), indicating favorable functional outcomes. We believe that biological reconstruction is a promising method for the treatment of malignant tumors of the wrist.

There are several case series for primary tumors of carpal bones (6,7). Ozturk et al. (20) reported that 46 (4%) of 1139 bone tumors were localized in the wrist. In our study, there were seven patients with carpal bone tumors (5 scaphoid, 2 lunate), all of which were identified as intraosseous ganglion cysts. Su et al. (21) stated that curettage and autologous bone grafting is an accepted treatment method for the treatment of intraosseous ganglion cysts of the carpal bone. In our study, six patients underwent curettage followed by autografting, and marginal excision was sufficient in 1 patient.

A giant cell tumor is a locally aggressive tumor and can locally recur. The literature reported a local recurrence rate of 3% to 28% for GCTs (22). In our study, 4 (11%) out of 36 patients with GCT developed local recurrence. Several authors reported that using local adjuvants (alcohol phenol, hydrogen peroxide, iodine) after benign tumor curettage can reduce local recurrence (23). Chemical adjuvants were not used in any patient in our series. However, we believe that GCTs can recur locally or even metastasize to the lung, and therefore these patients should be closely followed up.

The limitations of our study are due to its retrospective design and small sample size. The functional outcome assessment may be biased. That said, functional assessment is included in each outpatient follow-up in our oncology clinic. Although different tumor types were presented without subtyping, our study is strong in that it demonstrates the incidence of primary tumors of a rare localization.

CONCLUSION

To conclude, primary bone tumors rarely involve the wrist compared to the other parts of the skeletal system. In our study, wrist tumors were most commonly localized in the distal radius. The most common type of benign tumor was GCT, and the most common type of malignant tumor was Ewing sarcoma. By treating GCTs with curettage and cementing and malignant tumors with wide resection and FVFG, we were able to obtain favorable clinical, oncological, and functional outcomes. Further larger studies with longer follow-ups are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Marmara University Faculty of Medicine Clinical Research Ethics Committee (Date: 03.01.2020, Decision No: 09.2019.1033).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Carotid artery stenting: a single-center experience

Ali Burak Binboğa[1], Gökalp Güzel[2], Mehmet Onay[1], Çetin Murat Altay[1]

[1]Dr. Ersin Arslan Training and Research Hospital, Department of Radiology, Gaziantep, Turkey
[2]Dr. Ersin Arslan Training and Research Hospital, Department of Cardiovascular Surgery, Gaziantep, Turkey

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ABSTRACT

Aim: This study aimed to present the results of carotid artery stenting (CAS) in the treatment of patients with symptomatic and asymptomatic carotid artery stenosis (Cs).

Material and Method: Between September 2016 and June 2021, patients who underwent CAS in the interventional radiology department were reviewed, retrospectively. The demographic data of patients, comorbidities, carotid stenosis rates, and early and late complication rates after treatment were recorded from medical records. Acute stent thrombosis, stroke, and death in the first 30 days after CAS were considered early periprocedural complications. Doppler ultrasonography (USG) examinations were scanned at 6 months after the procedure and restenosis rates were investigated.

Results: There were a total of 113 patients; 31.2% female and 68.8% male. Symptomatic Cs was present in 62.8% (n=71) and asymptomatic Cs in 37.2% (n=42) of the patients. The technical success rate was determined as 98.2%. Micro-thromboembolism (n=4), pseudoaneurysm at the femoral insertion site (n=2), and acute stent thrombosis (n=1) were observed as early complications. Restenosis was detected 6 months after stenting in 1 patient (1.4%) with symptomatic Cs on Doppler USG. The mortality rate was 0.8% (n=1).

Conclusion: CAS is an effective and safe treatment method in symptomatic and asymptomatic patients with Cs.

Keywords: Carotid artery stenosis, carotid artery stenting, endovascular treatment, complication.

INTRODUCTION

Carotid artery stenosis (Cs) is an atherosclerotic disease that affects the extracranial carotid arteries, characterized by a decrease in lumen diameter and an increase in blood flow velocity (1, 2). Cs can be asymptomatic or cause a transient ischemic attack and acute ischemic stroke (2). Stroke is one of the leading causes of death and disability in adults worldwide (2). Although the prevalence of stroke in patients aged >45 years in Turkey varies according to region, it has been reported to be between 0.4% and 4.1% (3). Stroke is the second most common cause of death after ischemic heart disease and is responsible for 9% of all male deaths and 13% of all female deaths (4). Approximately 25-30% of all strokes are caused by Cs (5, 6). However, in recent years, there has been a decrease in the rate of deaths from stroke due to developments in both diagnosis and treatment methods (4).

Carotid artery stenting (CAS) and carotid artery endarterectomy (CAE) are the two main treatment modalities in the treatment of Cs. CAS is an endovascular treatment method, which has become an important alternative to CAE as a result of developments in stent technology (7-9). Due to the nature of CAS, short postoperative hospital stays and it is a minimally invasive method have made CAS more preferable. In patients with symptomatic and asymptomatic Cs, complication rates of CAS are acceptable compared to CAE. In addition, recent developments in the filter technology used to prevent stent and distal embolism, have increased the applicability of CAS more safely. However, the impact of these new developments on the periprocedural complication rates of CAS has not yet been adequately discussed.

This study aimed to present the results of CAS in the treatment of patients with symptomatic and asymptomatic Cs.

MATERIAL AND METHOD

This retrospective study was approved by Gaziantep University Clinical Researchs Ethics Committee (Date: 07.07.2021, Decision No: 2021/236). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Corresponding Author: Mehmet Onay, mehmetonay079@hotmail.com
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Patients

A retrospective review was made of patients who underwent CAS due to Cs in the interventional radiology clinic of Dr. Ersin Arslan Training and Research Hospital between September 2016 and March 2021. The demographic characteristics of the patients, such as age and gender, were recorded separately from the medical records. Patients with Cs who presented at the interventional radiology clinic with symptoms of transient ischemic attack (TIA), transient blindness (TB), syncope, and stroke were accepted as symptomatic Cs. The patients were separated into two groups as symptomatic Cs and asymptomatic Cs. Diagnostic digital subtraction angiography (DSA) images taken before CAS was used to diagnose Cs. The diagnosis of Cs on DSA images was made according to the criteria of "Equivalence of measurements of carotid stenosis (EMCS)" (10). Moreover, carotid plaque surfaces were classified according to DSA images as smooth plaque surface, irregular plaque surface, and plaque surface ulceration. Indications for CAS were determined according to the multi-society consensus guideline (11). In addition, comorbidities such as diabetes, hyperlipidemia, hypertension were recorded using pre-procedural patient evaluation records that are routinely kept in the clinic. The technical success, complication, morbidity, and mortality rates of the procedure were investigated in patients who underwent CAS due to symptomatic and asymptomatic Cs.

Carotid Artery Stenting

Heart rate, arterial blood pressure, and oxygen saturation were monitored throughout the procedure in all patients who underwent CAS. Brain diffusion-weighted magnetic resonance imaging (DAG MRI) was performed before CAS in all patients who underwent CAS, and the presence of acute - subacute stroke was investigated. These images were also used for comparison in patients with postprocedural neurological symptoms. All patients who underwent CAS were given 75 mg/day oral clopidogrel 5 days before the procedure or 300-450 mg oral clopidogrel was loaded 2 hours before the procedure if emergency CAS was to be performed. After the femoral

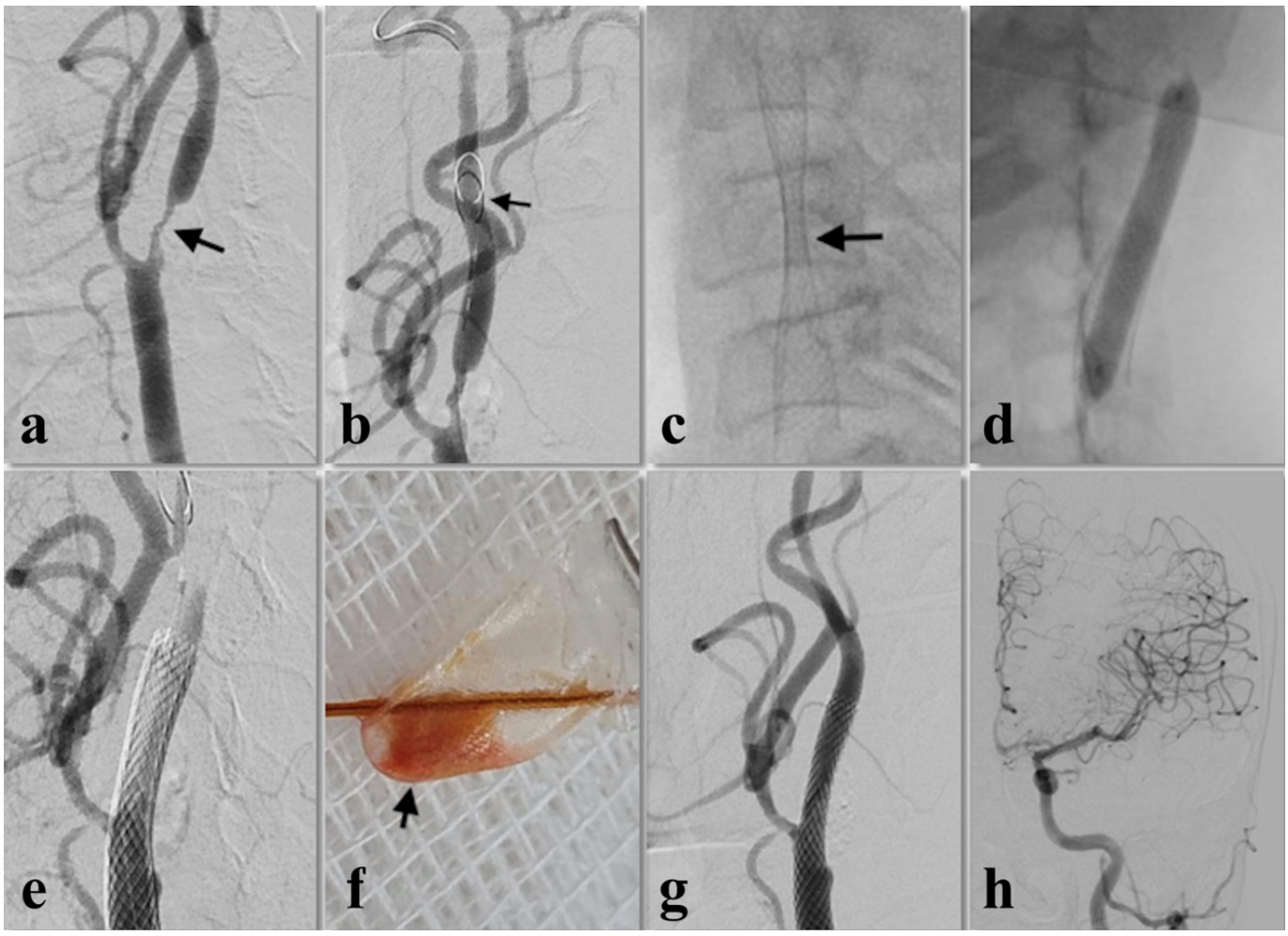

Figure 1: a-g (oblique) and h (anterior-posterior) DSA images show a 63-year-old male patient with symptomatic carotid artery stenosis. a shows long segment stenosis (black arrow). b shows the opened filter (black arrow) to prevent distal embolism. Afterward, the appropriately sized stent is opened. An hourglass appearance observes in c due to residual stenosis (black arrow). d demonstrates balloon angioplasty to obtain adequate patency. After balloon angioplasty, the control DSA image (e) is shown false occlusion in the distal ICA due to atheromatous plaques. In the same patient, the filter with atheromatous plaques is observed (f, black arrow). There is no residual stenosis (g) and no distal embolism (h).

artery puncture during the procedure, 5000 IU heparin was administered to maintain anticoagulation. In all patients, along vascular sheath (IVA 6F, 80 cm, Balt Extrusion, Montmorency, France or Neuron MAX 6F, 80 cm, Penumbra Inc., Alameda, California, USA) was placed and cannulated from the femoral artery to the target common carotid artery (CCA). After the target lesion in the internal carotid artery (ICA) was passed with appropriate microwire manipulations, a filter was placed approximately 3 cm distal to the lesion to prevent distal embolism in all patients. Then, a Wallstent (Boston Scientific Inc., Watertown, Massachusetts, USA) that has a closed-cell design, of appropriate diameter and length was advanced over the filter wire and the stent was opened. The residual stenosis rate was investigated on control DSA images, and balloon angioplasty was performed in patients with stenosis >30% to reduce the residual stenosis rate. In cases with bradycardia or a decrease in the basal heart rate of >20% due to vagal stimulation in the carotid body during angioplasty, 1 mg of atropine sulfate was immediately administered via the peripheral venous line. The filter was then removed and control DSA images were obtained for examination of possible thromboembolism in the intracranial arteries, and remove the filter. Then the procedure was terminated. An illustrative case was presented in Fig.1 a-h. All patients underwent a detailed neurological examination in the angiography suite after the procedure, and the presence of neurological symptoms due to possible distal embolism was investigated. All patients were hospitalized for one-day post-procedurally and vital values were monitored. Patients with no neurological signs and stable vital values were discharged with anti-aggregant drugs (clopidogrel 75 mg/day and acetylsalicylic acid 100 mg/day) for at least 6 months.

Follow-up

Doppler USG was performed in all patients at 6th-month after CAS. Restenosis was defined as >50% Cs. For patients with neurological symptoms, DWI MRI was performed and possible CAS-induced thromboembolism was investigated by comparisons with the DWI MRI scans taken before the procedure.

Statistics

Data were analyzed using IBM SPSS Statistics v. 23 software (IBM, Armonk, NY, USA). Descriptive statistics were stated as mean ± standard deviation (SD) for numerical variables, and as number (n) and percentage (%) for categorical variables. The difference between the two groups was examined with the Mann-Whitney U test, and the relationship between two categorical variables was examined with the Chi-Square test. A value of $p< 0.05$ was considered statistically significant.

RESULTS

The characteristics of the study population are summarized in **Table 1**. The total 113 patients comprised 31.2% females and 68.8% males, of which 62.8% (n=71) had symptomatic Cs and 37.2% (n=42) had asymptomatic Cs. The mean age of the patients was similar in symptomatic and asymptomatic groups ($p>0.05$). The rates of the Cs plaque morphology were 48.6% (n=55) smooth surface, 33.7% (n=38) irregular surface, and 17.7% (n=20) surface ulceration. The rates of plaque surface morphology in the patient's groups were detailed in **Table 1**. There was a statistically significant correlation between the plaque surface classification and the patients with symptomatic Cs ($p=0.016$).

Table 1. Patient and lesion characteristics

Variables	Symptomatic Cs n= 71 (%)	Asymptomatic Cs n=42 (%)	p
Age (years)±SD	66.06±8.22	68.07±9.19	0.49
Female	33 (46.4)	22 (52.3)	0.54
Male	38 (53.4)	20 (47.7)	
Stenosis rate			0.67
70-95%	48 (67.6)	30 (71.4)	
95-99%	23 (32.3)	12 (28.6)	
Plaque morphology			**0.01***
Smooth	33 (46.4)	22 (52.3)	
Irregular	20 (28.2)	18 (42.8)	
Ulceration	18 (25.4)	2 (4.9)	
Symptoms		-	NA
Stroke	31 (43.6)		
TIA	23 (32.3)		
TB	12 (17)		
Syncope	5 (7.1)		
HT	58 (81.6)	29 (69)	
HL	50 (70)	19 (45.2)	0.64
DM	53 (74.6)	20 (47.6)	
HT+HL+DM	42 (59.1)	16 (38)	**0.03***

Cs: Carotid artery stenosis, TIA: Transient ischemic attack, TB: Transient blindness, HT: Hypertension, HL: Hyperlipidemia, DM: Diabetes Mellitus, *: Statistically significant, NA: Not Available

Balloon angioplasty was performed in all patients because of residual stenosis after stent placement. In patients with symptomatic Cs, the most common symptom was the stroke that was ipsilateral with stenosis. The most common comorbidity in patients with both symptomatic and asymptomatic Cs was hypertension, and this was most frequently accompanied by diabetes. No statistically significant difference was determined between the patients in both groups in terms of hypertension, hyperlipidemia, and diabetes ($p>0.05$). Both hypertension and diabetes were determined in 67.6% (n=48) of patients with symptomatic Cs, and in

35.7% of the patient group with asymptomatic Cs (n=15). This dual comorbidity rate was similar in both groups (p>0.05). Patients with three comorbidities (hypertension, diabetes, and hyperlipidemia) were more common in the symptomatic Cs group. Three comorbidities were determined in 59.1% (n=42) of the symptomatic Cs group and 38% (n=16) of the asymptomatic Cs group (p<0.05).

Treatment, Complications, and Follow-up Results

Technical success was determined at the rate of 98.2%. CAS could not be performed in two patients with symptomatic Cs. In one of the patients with technical failure, a filter was placed, but dense circumferential calcific plaque and lateral angulation of the ICA orifice did not allow the stent to be positioned safely in the appropriate position. In the other patient, the target artery could not be reached endovascularly, due to an anatomic variation of the right brachiocephalic trunk, which was seen to be located more inferiorly in the aortic arch. Carotid artery endarterectomy was performed in these two patients.

The complication rate in the symptomatic patient group was higher than in the asymptomatic patient group, but was not statistically significant (p>0.05, **Table 2**). The complications were micro-thromboembolism (n=4), pseudoaneurysm at the femoral insertion site (n=2), and acute stent thrombosis (n=1), respectively (**Table 2**). Patients who experienced micro-thromboembolism intraoperatively had irregular plaque surface or plaque ulceration. Of the patients with micro-thromboembolism, 3 had weakness in the upper extremity contralateral to the lesion, and 1 had a speech impairment. Symptoms regressed in all patients with micro-thromboembolism and there was no permanent neurological deficit. When the two groups were compared in terms of micro-thromboembolism, there was no statistically significant difference (p=0.608). One of the two patients with pseudoaneurysm was treated percutaneously and the other was treated surgically. The patient with acute stent thrombosis presented at the Emergency Department with hemiplegia on the 7th day after CAS. Thrombus causing total occlusion in the stent was detected on Doppler USG, and it was learned that the patient had stopped taking the anti-aggregant drugs. This patient died after intensive care follow-up. All patients who underwent CAS for both symptomatic and asymptomatic Cs had a 6-month follow-up Doppler USG. Restenosis was detected 6 months after stenting in 1 patient (1.4%) with symptomatic Cs on follow-up Doppler USG. The rate of restenosis in this patient was between 50-69%, and as the patient was asymptomatic, a revision procedure was not considered.

Table 2. Comparison of treatment and follow-up results in both groups

Variables	Symptomatic Cs n= 69* (%)	Asymptomatic Cs n=42 (%)	p
Technical success rates	97.1%	%100	NA
Complications			0.62
Microembolism	3 (4.3)	1 (2.4)	
Acute stent thrombosis	1 (1.4)	-	
Pseudoaneurysm	1 (1.4)	1 (2.4)	
None	66 (92.9)	40 (95.2)	
Restenosis			NA
Yes	1 (1.4)	0	
No	68 (98.5)	42 (100)	

Cs: Carotid artery stenosis, *: Follow-up results were not included in the study because of technical failure in two patients, NA: Not Available.

DISCUSSION

Cs causes 15-20% of all ischemic strokes (12). Severe CAS of 70-99% stenosis can lead to recurrent ischemic events (12). Therefore, patients who are symptomatic or asymptomatic but with severe stenosis are *Candida*tes for revascularization treatments such as CAS or CAE (13). In a systematic review of guidelines for the management of asymptomatic carotid stenosis, CAS can be performed in asymptomatic patients with moderate-severe Cs (50-99% stenosis) to prevent future ischemic events (13). In our study, all asymptomatic patients had 70-99% stenosis. While CAE is a surgical treatment, CAS is a minimally invasive endovascular method. CAS has been performed more frequently than CAE in recent years, as a result of developments in-stent and catheter technology. Many studies in the literature have compared the results of CAS and CAE. The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) study reported the 4-year follow-up results of randomized CAS and CAE in 2502 patients with symptomatic or asymptomatic Cs (9). According to the results of the CREST study, it was stated that the rates of stroke and death after the procedure were higher in both symptomatic and asymptomatic patients in the CAS group than in the CAE group (9). In a randomized study comparing rates of ischemia in patients with symptomatic Cs, there was reported to be no difference between CAS and CAE (14). Recent meta-analyses have stated similar postprocedural complication rates for both CAS and CAE (15, 16). CAS is an effective treatment option in the prevention of stroke, which may cause long-term mortality or morbidity (12). Developments in-stent and catheter technology and increased operator experience may have led to better results in CAS in recent years. In markets open-cell design and closed-cell design stents were available. These two different stent cell designs exhibit clinical significance in terms of complication. Stabile et al. (17) investigated the impact of different types of carotid stents on clinical outcomes in 1,604 patients. They emphasized open-cell design may be associated with an increased

30-day stroke risk (17). Because atherosclerotic plaque components and microthrombosis can be jailed between the stent wall and carotid artery intima by closed-cells of the stent. In our department, we use a closed-cell design stent to decrease 30-day stroke risk. Symptomatic patients were more common in the current study population (**Table 1**). The most common symptoms of Cs are stroke, TIA, and TB (9). In this study, the most common symptom was a stroke, which was consistent with the literature. It is important that patients with Cs are symptomatic before the procedure because the most important factor affecting the postoperative complication rates of CAS is whether the patient is symptomatic or asymptomatic before stenting (9,15,16). Plaque morphology affects both whether the patient is symptomatic or not and the occurrence of intraoperative complications. Plaque stability and morphology links with plaque histopathology (18). The majority of stable plaque has a thick fibrous cap and exhibits low intraoperative complication rates (18). On the other hand, unstable plaques are more prone to embolic complications (18). Choi et al. (19) noted that plaque surface morphology on DSA was a highly sensitive marker of plaque instability during CAS. In our study, the patients with symptomatic Cs had irregular plaque surface and plaque ulceration more frequently than the patients with asymptomatic Cs. In addition, intraoperative complications were common in patients with irregular plaque surface and plaque ulceration. Our data were compatible with the literature.

Complication rates may increase in patients with symptomatic Cs. Vatan et al. (20) reported that the most common periprocedural complication of CAS is ischemic events. Roubin et al. (21) reported the rate of major stroke as 1% and the rate of minor stroke as 4.8% after CAS. In the current study, the rate of minor stroke was 4.3% in patients with symptomatic Cs and 2.4% in asymptomatic patients, which is consistent with findings in the literature. Although the rate of minor stroke in patients with symptomatic Cs was proportionally higher than in asymptomatic patients in this study, it did not reach statistical significance. Further studies with more patients are needed.

Another complication associated with stenting is acute stent thrombosis, which is a rare but fatal complication of CAS. According to the time of carotid stent thrombosis, it is seen in 3 different periods as acute (first 30 days after CAS), late (after 30 days), and very late (after 1 year) (22). Anti-aggregant medication is one of the most important factors in the prevention of stent thrombosis because, during stenting, damage occurs in atheroma plaque and the target artery endothelium (22, 23). Therefore, anti-aggregant medication is routinely recommended to all our patients undergoing CAS for the prevention of stent thrombosis. One patient in the current study had acute stent thrombosis, which was fatal due to the discontinuation of the anti-aggregant medication. This finding may emphasize the importance of anti-aggregant medication in line with the literature.

Stenting may also cause a foreign body reaction, and restenosis may occur as a result of wound healing reactions (24). Restenosis rates after CAS have been reported as 11.1% (25). In the current study, only one patient in the CAS group had restenosis at 6 months and did not require treatment. There may be several reasons why the current study results seem better than previous findings in the literature. There may have been an effect from the type of stent used and there could be differences in patient compliance with anti-aggregant medication. More comprehensive and comparative studies with more patients are needed.

The technical success rates of CAS vary according to the vascular anatomy of the patients. In particular, anatomical variations in the vascular structures from the groin to the target ICA or the tortuous course can have significant effects. Müller et al. (16) reported that the complex configuration of the aortic arch and the presence of wide-angle CCA affect technical success in patients undergoing CAS. A complex aortic arch and wide CCA angulation have been stated as risk factors for ischemic complications. In the current study, technical failure occurred in one patient due to challenging vascular anatomy. In another patient, the intense calcific load of the atherosclerotic plaque caused by Cs, wide CCA angulation, and low stent flexibility can be said to be the reasons for technical failure.

This study had some limitations, primarily the retrospective and single-center design. Another limitation was the relatively low sample size, which limited the interpretation of statistical data. Moreover, DSA could be performed in patients with re-stenosis to confirm the severity of the stenosis. But, Doppler US usually may be a sufficient examination for patients with re-stenosis. However, these limitations were not considered to detract from the value of the study as there are so few studies discussing the outcome of CAS in patients with symptomatic and asymptomatic Cs. Therefore, this study can be considered to contribute to the literature.

CONCLUSION

CAS is an effective and safe treatment option in symptomatic and asymptomatic patients with Cs. Although not at a statistically significant level, there tended to be fewer complications of CAS in patients with asymptomatic Cs compared to patients with symptomatic Cs. Nevertheless, there is a need for further studies involving more patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: This retrospective study was approved by Gaziantep University Clinical Researchs Ethics Committee (Date: 07.07.2021, Decision No: 2021/236).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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The effects of dual anti-platelet therapy on titanium implant osseointegration: an experimental study

Mehmet Ali Kobat[1], Serkan Dündar[2], Alihan Bozoğlan[2], Mehmet Ali Gelen[1], Tarık Kıvrak[1], Gökhan Artaş[3], Suna Aydın[4]

[1]Fırat University, Faculty of Medicine, Department of Cardiology, Elazığ, Turkey
[2]Fırat University, Faculty of Dentistry, Department of Periodontology Elazığ, Turkey
[3]Fırat University, Faculty of Medicine, Department of Pathology, Elazığ, Turkey
[4]Fethi Sekin City Hospital, Department of Cardiovascular Surgery, Elazığ, Turkey

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ABSTRACT

Aim: In this study, we aim to investigate the effect of dual anti-platelet agents on osseointegration by studying a sample of rats with titanium implants in their tibias.

Material and Method: The titanium implants were placed surgically to the left tibias of a sample group of 50 rats. After implantation, the rats were randomly divided into five groups: acetylsalicylic acid (ASA) (n =10), treated with 20 mg/kg of ASA; ASA+ clopidogrel (CLPD) (n=10), treated with 20 mg/kg of ASA and 30 mg/kg of CLPD; ASA+ prasugrel (PRSG) (n=10), treated with 20 mg/kg of ASA and 15 mg/kg of PRSG; ASA+ ticagrelor (TCGR) (n=10), treated with 20 mg/kg of ASA and 300 mg/kg of TCGR; and a control group (CNT) (n =10) received no further treatment following implant surgery. The experimental period lasted four weeks, during which all medications were administered with oral gavage. Concluding the experimental period, the animals were euthanized, and researchers collected blood serums and the implants, along with some surrounding bones, from each rats.

Results: Bone implant connection and bone filling ratios (%) were observed histologically and documented. The bone-implant connection and bone filling ratios of the rats do not show statistically significant differences between the groups examined (P>0.05).

Conclusion: In this study, it was shown that there was no bone healing problem between the antiaggregant given groups and between these groups and the control group. Too many people have to take single or double antiaggregant due to many diseases. We think that it is an important study in terms of knowing that bone healing will not be negatively affected when dental implants or other bone prosthesis procedures are applied to these patients. The results of this study should be supported by further research.

Keywords: Anti-platelet drugs, bone healing, bone-implant connection, dental implant osseointegration, dual antiplatelet theraphy

INTRODUCTION

Dual anti-platelet therapy (DAPT) consists of a combination of acetylsalicylic acid (ASA) and an oral P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel), and forms the basis of antithrombotic therapy after myocardial infarction (MI) or percutaneous coronary intervention (PCI)(1). In Europe, many older adults are DAPT patients, and their number is growing steadily. According to data from 2015, DAPT was in use for 1,400,000 PCI patients and 2,200,000 MI patients annually throughout Europe (2). DAPT helps prevent atherothrombotic events by reducing platelet aggregation. ASA, the primogenital anti-platelet agent, has been shown to reduce the incidence of recurrent major adverse cardiovascular events by 20% (3).

Acetylsalicylic acid irreversibly inhibits thromboxane A2 production by inhibiting cyclooxygenase 1. The available evidence suggests that 75-100 mg /day of ASA be prescribed daily for every patient with coronary artery disease (CAD), whether or not there is a history of MI (3). It is also recommended for use in the prevention of clot formation in other situations (4).

Clopidogrel is a thienopyridine derivative that is the same as prasugrel, which irreversibly blocks the P2Y12

Corresponding Author: Mehmet Ali Kobat, drmehmetalikobat@gmail.com
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adenosine diphosphate (ADP) receptor on platelets. This reduces platelet activation and aggregation, ultimately decreasing blood viscosity and increasing bleeding time (5). Clopidogrel is recommended in addition to ASA after coronary stenting, regardless of the type of stent, in a dosage of 75 mg daily for six months after proper loading (e.g. 600 mg loading or 75 mg therapy for five days). In cases of life-threatening bleeding or high bleeding risk, one to three months' treatment may be recommended (6).

Prasugrel like clopidogrel, prasugrel is an irreversible P2Y12 antagonist of the thienopyridine class; however, in vitro studies have shown it to be both faster and stronger (7). In patients with acute coronary syndrome (ACS) who undergoing PCI, prasugrel (60 mg loading dose, 10 mg/day maintenance dose) is primarily recommended in addition to ASA, according to ESC guidelines, unless there are contraindications (8).

Ticagrelor is a thienopyridine-group drug that blocks the P2Y12 receptor on the platelet, reversibly inhibiting platelet aggregation. Since it does not require metabolic activation, it is more effective than clopidogrel (9,10). In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) with ASA is recommended, even if treatment with clopidogrel has, unless there are contraindications (11). Although ASA and clopidogrel are sometimes used alone, a combination of clopidogrel, ticagrelor or prasugrel with ASA is recommended after coronary artery disease, ACS and coronary stenting (6).

Dental implant-supported prostheses are a scientifically proven treatment option for people with dental deficiencies like edentulism. Many factors are known to affect wound and bone healing. As for osseointegration, defined as the integration of bones and implants, the main factors impacting its success are the quality and amount of bone placed in the dental implant;, the patient's systemic diseases, smoking and drug use or lack thereof; and the geometrical and surface features of the implant device (12,13). Osseointegration is critical for a dental implant's success. Research and technological developments in the field of oral implantology have focused on the points affecting osseointegration. Bone healing is principal in dental implant surgery, as in all branches of bone surgery. Osseointegration and the quality of peri-implant bone tissue play a guiding role in the dental implant-supported prosthetic treatment. Infections, loss of function, and pain are a few of the problems that could lead to the failure of the implant during the bone healing process. On the other hand, some circumstances and applications that can positively affect this process may contribute to more successful dental implant outcomes (12,13).

To our knowledge, there are no previously existing studies evaluating the effects of dual anti-platelet therapy on osseointegration. However, controversial studies have continues to suggest the impact of antiaggregant use on bone healing. As such, identifying pharmacological agents that can affect bone healing continues to be a current issue. This study aims to evaluate the effects of systemic anti-platelet applicaitons on the osseointegration of titanium implants placed in rat tibias.

MATERIAL AND METHOD

Animals and Experimental Design

All experimental and surgical procedures in this study were performed in Elazığ, Fırat University Experimental Research Center in Elazığ, Turkey. The study was approved by the Fırat University Animal Experimental Ethics Committee on January 10, 2020 (Protocol Number: 371066). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

In this study, 50 healthy adult female Sprague-Dawley rats aged 3–3.5 months were used. The average weight of each rat at the start of the experiment was 240–260 grams. The rats were kept in plastic containers, whose temperatures were checked daily. During the experiment, the rats were not limited in terms of food and water, and the light cycle in the lab was adjusted to rotate through 12 hours of darkness and 12 hours of brightness. All of the rats were selected in the same estrus period to ensure standardization throughout the experimental protocols (13).

Titanium implants (Implance Dental Implant System, AGS Medical Corporation, İstanbul, Turkey,) were surgically inserted into the rats' tibias, following which they were randomly divided into five groups with similar mean weights in each group: the control (CNT) group (n=10), the ASA group (n=10), the ASA+Clopidogrel (ASA+CLPD) group (n=10), the ASA+Prasugrel (ASA+PRSG) group (n=10) group, and the ASA+Ticagrelor (ASA+TCGR) (n=10) group. In the CNT group, the rats received no further treatment during the experimental period following implant surgery. In the experimental ASA group, they were given 20 mg/kg per day of ASA; in the ASA+CLPD group, they were given 20 mg/kg of ASA and 30 mg/kg of clopidogrel per day; in the ASA+PRSG group, they were given 20 mg/kg of ASA and 15 mg/kg of prasugrel per day; and in the ASA+TCGR group, they were given 20 mg/kg of ASA and 300 mg/kg ticagrelor per day. All medication was administered via oral gavage (14). Four weeks after implant placement, the animals were euthanized (12,13).

Surgical Procedures

All of the rats included in this study were given antibiotic prophylaxis intramuscular injections of 50 mg/kg penicillin 30 minutes before general anesthesia. Xylazine (5 mg/kg, Rompun, Bayer, Germany) and Ketamine hydrochloride (50 mg/kg, Ketasol, Richter Pharma, Wels, Austria) were injected intramuscularly into the rats, and general anesthesia was accomplished. Much attention was paid to sterilization during all surgical procedures. After were anesthetized, the surgical site was shaved and cleaned with povidone-iodine. An incision approximately 10–15 mm in length was made along the left tibial crest. The soft tissues were separated, and the tibia metaphyseal bone was exposed. Implant beds were adjusted with a drill with saline perfusion. The titanium implant was then placed in the metaphyseal part of the left tibia with primarily stabilized. The titanium implants we used were 4 mm long and 2.5 mm in diameter (grade 4 titanium, machined surface, TiAI6V4). After the titanium implants were placed, the flaps were returned to their original positions, and the layers were sutured using vicryl 5-0 (12,13).

Histologic Procedures and Analysis

The original integrated implants and surrounding bone tissue were used for the subsequent histomorphometric and immunohistochemical analyses. All samples were kept in 10% formaldehyde when initially taken and then transferred to 10% formic acid after to soften the tissues. After the surrounding tissues were softened, the implants were carefully removed from the samples. The samples were dried and embedded in paraffin wax. Finally, they were staining with hematoxylin and eosin for microscopic analysis. Sections of 6 μm in thickness, corresponding to the implants with surrounding bone tissue area, were evaluated by light microscopy (15).

Histological staining for bone–implant connection (BIC) and bone filling (BF) analysis was performed using the hematoxylin and eosin extracted from the samples. BIC and BF were examined using a light microscope and image analyzer at the Department of Pathology Laboratories, Faculty of Medicine, Firat University, Elazig, Turkey. Histomorphometry was performed by the same specialist using stereological software. The BIC ratio (or percentage) of each specimen was measured as the ratio of implant surface directly touching the bone compared to the total implant surface length. The BF ratio (or percentage) was measured by calculating the bone-filled area's distance 0.5 mm from the implant (the medial, distal and apical portion of the implant) (12,13). Researchers used the Olympus DP71 software imaging system for the histological analysis.

Biochemical Analysis

While the rats were anesthetized, blood samples were obtained through cardiac puncture to measure the serum alkaline phosphatase (ALP), calcium (Ca), phosphorus (P), blood urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and magnesium (Mg). Biochemical data were measured for each rat at the Central Biochemistry Laboratory of the Faculty of Medicine, Fırat University.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 22.0). The appropriateness of the normal distribution of the parameters was assessed by the Kolmogorov–Smirnov test. A one-way analysis of variance (one-way ANOVA) was performed for the parameters, showing a normal distribution. Tukey's Honestly Significant Difference test was used to detect which group caused the difference. Continuous data were presented as mean±standard deviation values, and numerical measurements were presented as median, minimum, and maximum values. A statistical significance level of 95% ($P<0.05$) was adopted.

RESULTS

After the four-week experimental period, a rat in the ticagrelor group died. Apart from this, no systemic or wound-related problems were observed in the rats.

The BIC ratios of the rats in the ASA group were lower than those of the rats in the control and other groups, but not to a statistically significant extent ($P>0.05$) (**Table 1**). Statistically, significant differences were not detected between the groups in terms of their relative BF ratios ($P>0.05$) (**Table 2**). Biochemical results (BUN, Cr,C AST, ALT, Ca, ALP, P and Mg) were similar between groups ($P>0.05$) (**Table 3**) (**Figure 1**).

Table 1. Bone implant connection ratio (%) of the groups

	Mean±Std. deviation	p
Control (n=10)	61.00±15.23	>0.05
ASA (n=10)	50.20±17.39	>0.05
ASA+Klopidogrel (n=10)	66.50±18.41	>0.05
ASA+Prasugrel (n=10)	63.00±14.94	>0.05
ASA+ticagrelor (n=9)	60.00±18.20	>0.05

Table 2. BF ratio (%) of the groups

	Mean±Std. deviation	p
Control (n=10)	62.00± 9.77	>0.05
ASA (n=10)	61.00± 15.23	>0.05
ASA+Klopidogrel (n=10)	62.50± 16.54	>0.05
ASA+Prasugrel (n=10)	60.50± 15.17	>0.05
ASA+ticagrelor (n=9)	57.77± 16.97	>0.05

Table 3. Biochemical parameters in groups

	CNT (n:10)	ASA (n:10)	ASA+CLPD (n:10)	ASA+PRSG (n:10)	ASA+TCGR (n:9)
BUN (mg/ dL)	62.00±9.77	62.00±9.77	62.50±16.54	60.50±15.7	57.77±16.97
Creatinine (mg/dl)	.40±.08	.39±.08	.40±.03	.39±.06	.39±.06
AST(U/L)	211.10±27.56	222.40±24.71	198.80±21.75	206.90±18.32	213.33±16.26
ALT(U/L)	68.40±6.04	74.10±9.06	66.80±6.33	75.20±11.94	75.88±12.45
Calcium (mg/dl)	9.24±.86	9.41±.52	9.57±.74	9.45±.78	9.00±.72
Magnesium (mEg/L)	2.03±.19	2.09±.13	1.97±.12	1.94±.14	1.95±.21
ALP(U/L)	103.90±4.65	112.20±16.15	112.60±15.26	109.80±18.12	112.22±26.57
Phosphorus (mg/dl)	6.09±.96	7.04±.67	6.47±.58	6.20±.58	6.67±.66

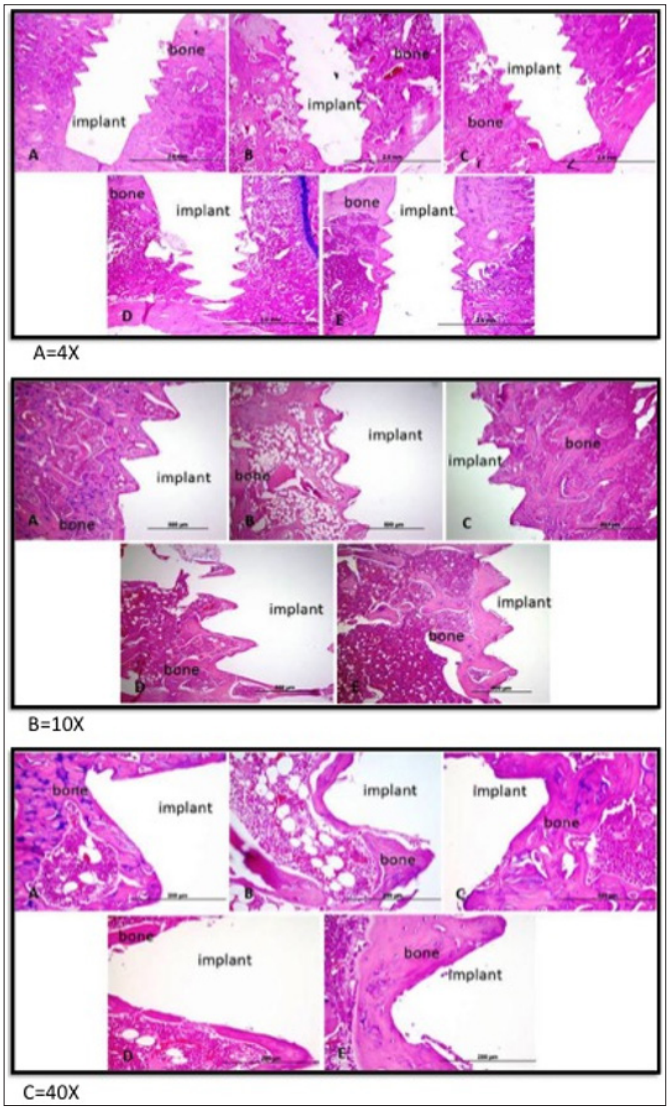

Figure 1. Decalcified histologic images of the A: Control B: Asetilsalisilic acid (ASA), C: ASA+Klopidegrol, D: ASA+Prasugrel, E: ASA+Ticagrelor Group, (F=4X magnification, Hematoxilen Eosine, G=10X magnification, Hematoxilen Eosine, H=40X magnification, Hematoxilen Eosine,). Implant surface not contacting bone (α), Implant surface in contacting with the bone (β), Total implant surface: £, Bone Implant Contact Ratio (%): £-α(β)/£. Bone filling detected by measuring the bone filled areas distances 0.5 mm from implant (the medial, distal and apical portion of implants). Bone filling areas (à), non-bone areas (ë), total area (Ă). Bone filling Ratios (%):Ă-ë/Ă (à/Ă).

DISCUSSION

Long-term ASA therapy is beneficial in reducing the risk of subsequent MI, stroke, and vascular death among patients with a wide range of cardiovascular disease symptoms; yet concerningly, Vestergaard P et al. (16) showed that patients using ASA experienced more bone fractures. This increased bone fracture rate was lower in people using low doses of ASA (17). In our study, while BF rates were similar, BIC rates were lower in the group receiving ASA compared to other groups, but the difference was not significant. The use of antiaggregant ASA (75-325 mg/d) was not found to have a negative effect on bone healing. Similarly, Hunter et al. (18) found no difference observed between bone healing of ankle fractures in the 6-month follow-up of patients using ASA postoperatively to treat their pain.

Different results have been obtained in previous studies on bone healing for patients taking clopidogrel. In our study, the osseointegration level in the ASA and clopidogrel group was similar to that of the control and other groups. Syberg et al. (19) showed that clopidogrel treatment in adult ovariectomized mice for four weeks resulted in a significant reduction of trabecular bone volume, alongside a reduction in trabecular number in tibial and femur bone tissues compared with control group animals. In contrast, Su et al. (20) reported that treating adult ovariectomized mice with high dosages of clopidogrel resulted in a significant increase in trabecular bone volume in the tibia and significantly decreased serum levels of osteoclast activity marker when compared to vehicle-treated control mice. Additionally, Lillis et al. (21) reported that bone healing was further along in a sample group of rabbits receiving six weeks of clopidogrel treatment for in circular calvarial defect.

In the group given ASA and prasugrel, the BIC and BF ratios were similar to the control group and other groups. There was no difference in terms of bone healing. There are no studies we could find in the literature investigating the effect of prasugrel or ASA+prasugrel on bone healing.

In our study, no significant difference was observed between the group receiving ASA and ticagrelor and the control and other groups in terms of osseointegration. There is only one study we could find in the literature investigating the effect of ticagrelor on bone healing. Mediero et al. (22) showed that ticagrelor inhibited osteoclast differentiation and promoted osteoblast differentiation in vitro. Ticagrelor promotes bone formation by regulating osteoclast and osteoblast functions in vitro with an adenosine-induced mechanism.

CAD has reached almost epidemic rates in most societies and causes more deaths than all other cardiovascular disease groups (23). CAD and peripheral artery disease require the use of ASA for life. In addition, ASA is used in ischemic stroke, transient ischemic attack and pre-eclampsia treatments (4). The P2Y12 inhibitor(s) used with ASA after acute MI or PCI must be taken for a period of six months to one year. Meanwhile, dental implantation is a suitable treatment method for those who have lost teeth or who are completely toothless, and many patients who have planned to receive implant treatment use single or double antiaggregants.

Not knowing how bone healing will proceed due to possible negative interactions with other medication can cause hesitation and sometimes delay treatment for patients seeking implants. However, prior to our writing, there were no studies readily available which showed the presence or absence of a relationship between antiaggregant use and bone healing after the dental implant procedure.

We found no difference between the various antiaggregant agents as they related to the osseointegration of titanium implants in rat tibias, nor was there a significant difference when they were applied versus in the control group. This result will contribute to the literature and to clinical practice by allowing consulting surgeons to more comfortably proceed with dental implantation when patients are undergoing DAPT.

Our study has several limitations. First, anti-platelet was not applied before the procedure. Second, our use of rats is a necessarily imperfect analog for similar drug pathways and health outcomes in humans. Third, in this study, we could not investigate the effects of long-term anti-platelet use on bone healing since there was no longer follow-up. Finally, long bones (tibia-femur) and craniofacial bones (mandibula-maxilla) have different osteogenic potential; therefore, antiaggregant use may respond differently on craniofacial bones (13).

CONCLUSION

This study showed that daily anti-platelet uses during the 28-day experimental period did not affect bone-implant contact and bone filling ratios in for titanium implants in rat tibias. However, more extended studies are needed to clarify whether anti-platelet use affects osseointegration in the bones of the face and during longer periods of time.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Fırat University Animal Experimental Ethics Committee on January 10, 2020 (Protocol Number: 371066).

Informed Consent: Since the study was an animal experiment, approval was obtained from the animal experiment ethics committee.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Postoperative analgesic effectiveness of bilateral erector spinae plane block for adult cardiac surgery: a randomized controlled trial

Bülent Barış Güven, Tuna Ertürk, Ayşin Ersoy

University of Health Sciences, Sultan 2. Abdulhamid Han Training and Research Hospital, Department of Anesthesia and Reanimation, İstanbul, Turkey

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ABSTRACT

Introduction: There are few randomized controlled trials examining the effectiveness of bilateral Erector Spinae Plane Block (ESP) with patients undergoing cardiac surgery. The effect of bilateral ESP block on postoperative pain levels and analgesic consumption for patients undergoing open-heart surgery was examined in this single-blind, randomized, controlled trial.

Material and Method: 54 patients who underwent cardiac surgery with open median sternotomy under general anesthesia between May 2020 and June 2021 were included in the study. Patients were randomized into two groups, each consisting of 27 patients, one with 40 ml of 0.25% bupivacaine and bilateral ESP block, the other with no block implementation (control group). Demographic data, operation type, length of stay in the Intensive Care Unit (ICU), numerical rating scale (NRS) values in the first 24 hours after extubation, and morphine consumption values of the patients were recorded for the study.

Results: In the study, 4 patients were excluded from follow-up due to prolonged intubation in the postoperative period. The data of a total of 50 patients (ESP group n=25; Control group n=25) were analyzed. The duration before first analgesic (mean±SD: 459.2±92.8 min.) of the ESP group was statistically longer than those in the control group (mean±SD: 142.0±56.6 min.) ($p<0.001$). The total length of stay in the ICU and rate of nausea-vomiting were lower for the ESP group than for the control group ($p<0.05$). Total morphine consumption (mean±SD: 5.1±3.1 mg) of the ESP group in the first 24 hours was statistically lower ($p<0.001$) compared to the consumption of the control group (mean±SD: 14.8±4.2 mg). NRS scores were significantly lower for the ESP group at postoperative 1st, 2nd, 4th, 6th, and 8th hours compared to the control group ($p<0.05$).

Conclusion: ESP block applied bilaterally in adult cardiac surgeries decreased postoperative pain scores and morphine consumption. At the same time, it was observed that the length of stay of the patients in the ICU was reduced and there were no complications.

Keywords: Erector spinae plane block, cardiac surgery, postoperative pain, ultrasound guidance, fascial plane block

INTRODUCTION

In order to reduce hospital stay after open heart surgeries and improve clinical outcomes, multimodal and multidisciplinary approaches that standardize perioperative care are targeted for development (1). The most important of these approaches developed with enhanced recovery after surgery (ERAS) protocols is to provide adequate pain control with a multimodal approach in order to reduce cardiac-pulmonary complications and postoperative opioid consumption. A multimodal pain management plan should include non-opioid systemic analgesic agents, regional anesthesia techniques, and minimal use of opioids (2).

Thoracic epidural analgesia (TEA), one of the regional anesthesia techniques, has been widely used for cardiac surgeries and has been shown to be effective to relieve postoperative pain (3). However, the risk of possible development of neuraxial hematoma due to perioperative heparinization and the high incidence of hypotension limits the use of TEA. Paravertebral block (PVB) has been applied bilaterally for sternotomy pain for cardiac surgeries, and it has been reported that it reduces the need for opioids in the postoperative period by reducing pain scores and is safer than TEA due to heparinization (4,5). However, there are risks associated with PVB such as pneumothorax, vascular

Corresponding Author: Bülent Barış Güven, barguv@gmail.com

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injection, and intrathecal injection. The erector spinae plane (ESP) block, which has less such risks and is more easily applicable, is a new interfacial plane block that has been studied a lot recently and is promising in this regard.

It has been shown in many studies that ultrasound-guided ESP block is effective and can be applied safely in chest, abdominal, vertebral, and lower extremity surgeries (6). There are very few randomized controlled trials in the literature examining the effectiveness of ESP block for patients undergoing cardiac surgery. For this single-blind, randomized, controlled trial, it was aimed to examine the effect of bilateral ESP block on postoperative analgesic consumption and pain levels of patients undergoing open heart surgery.

MATERIAL AND METHOD

This study was designed as a prospective, randomized, single-blind, controlled trial and the study was approved by University of Hamidiye Clinical Research Ethics Committee (Date: 27.02.2020, Decision No: 2020.02.27-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The inclusion criteria for 66 patients were: being 18-65 years old, being identified as American Society of Anesthesiologists (ASA) physical status classes I or II, having body mass index (BMI) 20 to 30 kg/m², undergoing any of the coronary artery bypass graft (CABG), atrial septal defect (ASD) repair and heart valve replacement operations by opening a median sternotomy under general anesthesia (**Figure 1**). Patients who underwent two or more surgical procedures in the same operation were not included in the study due to the concern that such combined procedures may increase the duration of the operation and cause differences. Patients with emergency surgery, ASA-3 and above, spinal deformities, failed blocks, bleeding diathesis, local anesthesia allergy, neurological deficit, chronic painkillers, or narcotic drug use as well as patients taking antithrombotic drugs and patients with abnormal coagulation parameters were excluded from the study.

One day before the operation, the patients were informed about the use of the ESP block, the 11-point numerical pain rating scale (NRS), and patient-controlled analgesia (PCA) device, and their written informed consent was obtained in this regard. The patients were randomized using the closed-envelope method and divided into two groups (1:1 allocation ratio). All patients were premedicated with 0.03 mg.kg-1 midazolam on the day of surgery; and then, the patients were taken to the operating room and standard monitoring including SpO_2, ECG, non-invasive blood pressure monitoring was applied to all patients. Before general anesthesia, patients in the ESP group were placed in a sitting position for the ESP block and the procedure area was sterilized. A 10-5 MHz Linear probe and an 80-mm B.Braun Stimuplex peripheral block needle were used under the guidance of real-time USG (SonoSite M-Turbo). The USG probe was placed approximately 3 cm lateral to the T5 spinous process, in the parasagittal plane. After local infiltration with 2% lidocaine, the block needle was advanced in the craniocaudal direction with an in-plane approach at an angle of 30 degrees from the skin. When the needle reached the T5 transverse process by passing the trapezius, rhomboid major and erector spinae muscles, 1 ml of normal saline was injected (hydrodissection) between the erector spinae muscle fascia and the transverse process. After confirming the location of the needle in this way, ESP block was applied by administering 20 ml of 0.25% bupivacaine to the same plane after negative blood aspiration (**Figure 2**). This process was applied to the other side in the same way. All of the ESP blocks in the study were performed by the same anesthesiologist (B. B. G.). ESP block was not applied to the patients in the control group. General anesthesia was induced by intravenous (IV) administration of 1 $\mu g.kg^{-1}$ fentanyl, 0.15 $mg.kg^{-1}$ midazolam, 1-2 $mg.kg^{-1}$ propofol and 1 $mg.kg^{-1}$ rocuronium to the patients of both groups. Maintenance of anesthesia was achieved with inhaled sevoflurane in an air-oxygen mixture with 50% inspired oxygen concentration, rocuronium infusion (0.01 $mg.kg.min^{-1}$) and fentanyl infusion (2-3 $\mu g.kg.h^{-1}$). At the end of the operation, 1 g IV paracetamol, 100 mg IV tramadol and 8 mg IV ondansetron were administered to all patients. After the operation, IV PCA device prepared with morphine (0.5 mg/ml concentration, 1 mg bolus dose, 10 min lock-in time) was inserted for patients of both groups after the operation. The nurses who filled out the patient follow-up form in the postoperative period were blind to the study and routinely administered 1 g IV paracetamol every 8 hours in the postoperative period to all of the patients. For patients with NRS >4, 1 mg morphine IV bolus was administered via PCA as a rescue analgesic dose.

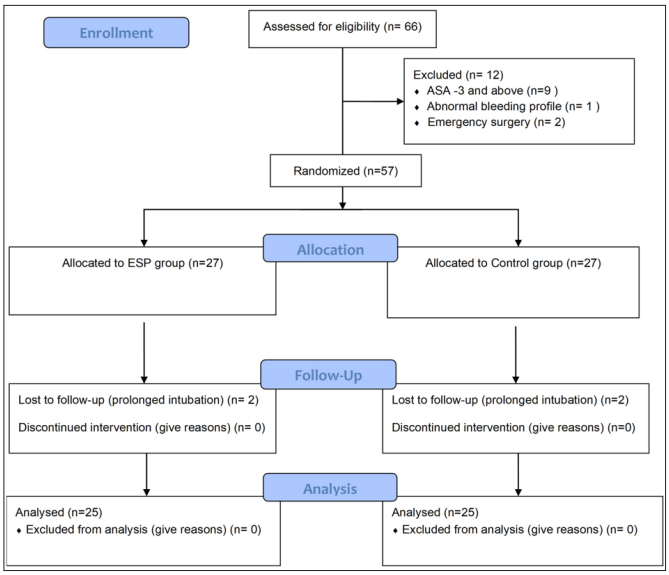

Figure 1. CONSORT Flow Diagram

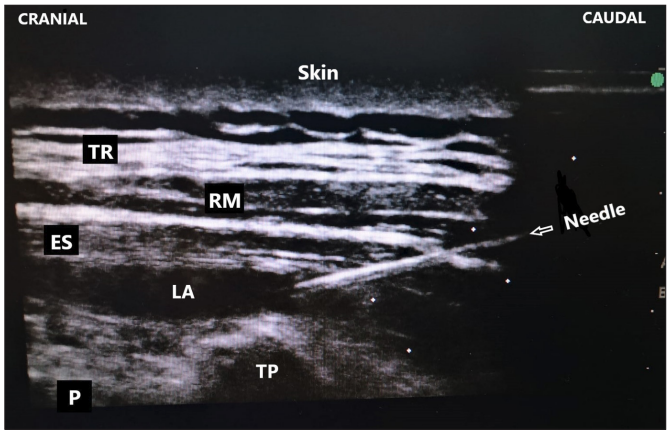

Figure 2. Ultrasound-guided erector spinae plane (ESP) block.
TR: Trapezius muscle; RM: Rhomboid major muscle; ES: Erector spinae muscle; LA: Local anesthetic drug; TP: Transverse process; P: Pleura

Hourly and total analgesic consumption during the postoperative 24 hours was the primary target in the study. The duration before the first rescue analgesic, the 11-point NRS (0-10, 0 for no pain and 10 for worst pain), mechanical ventilation duration, ICU length of stay, the incidence of postoperative nausea or vomiting (PONV) were considered as secondary targets. NRS scores were recorded at hourly periods of 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 after extubation. In the meantime, local anesthesia toxicity and complications related to ESPB (hematoma, infection and pneumothorax) were recorded.

Statistical Method

The power analysis of the study was based on the study of Nagaraja et al. (7) on ESP block. The standard effect size was determined as 0.8 with 5% margin of error and 80% power, and a total of 66 patients were included in the study. The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured with the Kolmogorov Smirnov test, and the independent samples t test and the Mann-Whitney u test were used in the analysis of quantitative independent data. The chi-square test was used for the analysis of qualitative independent data, and the fischer test was used when the chi-square test conditions were not met. The analysis was carried out using the SPSS 27.0 program.

RESULTS

66 patients who underwent CABG, ASD repair, aortic valve replacement (AVR), and mitral valve replacement (MVR) operations by opening median sternotomy under general anesthesia in the Cardiovascular Surgery OT of Sultan 2. Abdülhamit Han Training and Research Hospital between May 2020 and June 2021 were included in the study. Of these patients, 9 patients with ASA3 and above, 1 patient who underwent emergency surgery, and 2 patients with abnormal bleeding profile were excluded from the study. 54 patients were randomized and divided into two groups as the ESP applied group (n=27) and the control group (n=27). The data of 4 patients whose postoperative intubation duration was prolonged (>6 hours) were not used for the analysis (**Figure 1**). Thus, the data of a total of 50 patients from 25 patients in both groups were statistically analyzed.

Age, sex distribution, height, weight, BMI, and European System for Cardiac Operative Risk Evaluation-2 (Euro Score-2) values of the patients did not differ significantly (p>0.05) between the ESP block group and the control group. There was no significant difference (p>0.05) between the two groups in terms of duration of surgery, type of surgical operation, duration of cardiopulmonary bypass (CPB) and intraoperative total fentanyl consumption (**Table 1** and **Table 2**).

Table 1. Demographic Data

Characteristic	ESP group (n=25)	Control group (n=25)	p value
Age (year)	50.6±16.8	58.7 ±12.9	0.063
Gender (male /female)	14/11	12/13	0.560
Weight (kg)	77.2±16.2	80.8 ±14.4	0.415
Height (cm)	169.5±7.7	167.8±7.0	0.410
BMI (kg/m²)	26.7±4.3	28.6±4.1	0.118
Duration of surgery (min)	157.2±21.6	160.4±21.4	0.606
Euro Score-2	3.1±3.9	3.0±4.0	0.648
Type of surgery			
CABG	16 (64%)	17 (68%)	0.765
MVR	6 (24%)	5 (20%)	0.733
ASD	2 (8%)	1 (4%)	1.000
AVR	1 (4%)	2 (8%)	1.000

Data are expressed as mean±standard deviation or number (proportion), Euro Score: European System for Cardiac Operative Risk Evaluation, CABG:Coronary artery bypass graft, MVR: Mitral valve replacement, ASD: Atrial septal defect, AVR: Aortic valve replacement, Min: Minute.

Table 2. Intraoperative and postoperative variables between the groups

Variable	ESP group (n=25)	Control group (n=25)	p value
CPB time (min)	74.1±17.7	75.6±18.3	0.760
IO total fentanyl consumption (mcg)	548±89.5	560±99	0.588
PO total morphine consumption in 24 hour (mg)	5.1±3.1	14.8±4.2	0.000*
Total duration of MV in the ICU (min)	254.0±36.5	326.4±29.1	0.001*
Time to ambulation (hour)	28.8±6.7	37.4±9.6	0.001*
Total length of stay in the ICU (hour)	46.7±9.0	55.3±11.8	0.005*
Time to first use of PCA (min)	459.2±92.8	142.0±56.6	0.000*
Incidence of PONV in 24 hour	6/25	1/25	0.042*

Data are expressed as mean±standard deviation or number, CPB: Cardiopulmonary bypass, IO: Intraoperative, MV: Mechanical ventilation, PO: Postoperative, Min: Minute, ICU: Intensive care unit, PCA: Patient-controlled analgesia, PONV: Postoperative nausea and vomiting. *p < 0.05= statistical significance

Mechanical ventilation (MV) duration and duration before mobilization in the ICU were found to be significantly shorter for the ESP group compared to the control group ($p<0.05$). The mean duration before first analgesic was 459.2±92.8 minutes for the ESP group, and 142.0±56.6 minutes for the control group. This difference was statistically significant ($p<0.001$). The total length of stay in the ICU and rate of nausea-vomiting were significantly lower ($p<0.05$) for the ESP group compared to the control group (**Table 2**).

While total morphine consumption in the first 24 hours was 5.1±3.1 mg for the patients with ESP block, this consumption was found to be 14.8±4.2 mg for the control group, and this difference was statistically significant ($p<0.001$). Morphine consumption amounts at the postoperative 1st hour, 2nd hour, 4th hour, 6th hour, 8th hour, 12th hour, 16th hour and 20th hour were significantly lower ($p<0.05$) for the ESP group compared to the control group. The amount of morphine consumption at the 10th and 24th hours did not differ significantly ($p> 0.05$) between the two groups (**Table 2** and **Table 3**).

Postoperative 1st hour, 2nd hour, 4th hour, 6th hour, and 8th hour NRS scores of the ESP group were significantly ($p<0.05$) lower than the scores of the control group (**Figure 3**). The 10th hour, 12th hour, 16th hour, 20th hour and 24th hour NRS scores did not differ significantly ($p> 0.05$) between the two groups (**Table 3**).

Table. 3 Comparison of the groups in terms of numeric rating scale (NRS) scores and morphine consumption after extubation

	ESP group	Control group	p Value
NRS scores			
1st hour	1.2±1.3	5.0±1.7	0.000*
2nd hour	1.2±1.0	3.5±1.3	0.000*
4th hour	2.1±1.4	4.2±1.8	0.000*
6th hour	2.4±1.8	4.2±1.6	0.000*
8th hour	2.2±1.7	4.1±1.7	0.001*
10th hour	4.2±2.2	4.4±1.3	0.751
12th hour	4.5±1.6	4.6±1.5	0.842
16th hour	4.2±1.6	4.5±1.4	0.679
20th hour	4.1±1.2	4.2±1.3	0.976
24th hour	4.4±1.2	4.4±1.1	0.832
Morphine consumption (mg)			
1st hour	0.2±0.5	2.8±1.2	0.000*
2nd hour	0.2±0.5	2.0±0.7	0.000*
4th hour	0.1±0.3	1.8±1.1	0.000*
6th hour	0.3±0.5	1.4±0.8	0.000*
8th hour	0.2±0.5	1.2±0.8	0.000*
10th hour	1.2±0.9	1.3±0.6	0.722
12th hour	0.6±0.6	1.1±0.7	0.008*
16th hour	0.9±0.6	1.3±0.6	0.050*
20th hour	0.9±0.6	1.3±0.6	0.018*
24th hour	0.6±0.6	0.5±0.6	0.598

Data are expressed as mean ± standard deviation, NRS: Numeric rating scale, *p<0.05= statistical significance

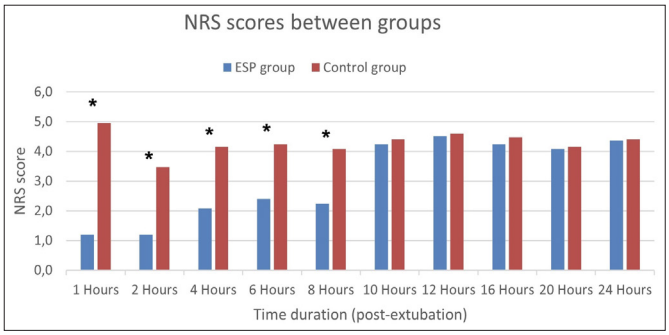

Figure 3. The mean values of the numerical rating scale (NRS) scores between the ESP group and the control group for postoperative pain at different time intervals. (*p < 0.05= statistical significance)

During the study, no complications such as local anesthesia toxicity or nerve damage, hematoma, pneumothorax, and infection that can be associated with ESP block were observed among patients who underwent ESP block operation.

DISCUSSION

For this prospective, randomized controlled trial, it was aimed to evaluate the effects of USG-guided bilateral ESP block in terms of postoperative pain level, morphine consumption, ICU length of stay, and complications in CABG, ASD repair, AVR and MVR operations. As a result of this study, a significant decrease was determined for the morphine consumption in the first 24 hours and for the NRS scores in the first 8 hours postoperatively for patients who underwent ESP block operation. Along with this decrease in opioid consumption, a significant decrease was found in ICU length of stay, incidence of nausea-vomiting, and MV durations.

Median sternotomy is the most commonly used incision in open heart surgeries and provides the clearest view for the surgeons. It has been reported that 30-75% of patients undergoing median sternotomy experience moderate level pain in the postoperative period, and chronic pain syndrome develops for more than 4% of such patients (8). In cardiac surgery, especially for patients with limited cardiac reserve, postoperative pain may cause poor clinical outcomes by stimulating the sympathetic nervous system. At the same time, opioid drugs used systemically to relieve pain may contribute to this poor outcome with their side effects such as prolonged sedation, respiratory depression, ileus, nausea, and vomiting (9). Although minithoracotomy techniques have been developed recently against such concerns, median sternotomy is still the gold standard incision in cardiovascular surgeries. In order to reduce the postoperative pain of this type of incision, new pain management techniques including TEA, PVB, Parasternal block and pecto-intercostal fascial block have been developed in recent years (3,4,10,11). Since

the sternum is innervated by T2-T6 intercostal nerves, none of these techniques alone can be expected to produce adequate analgesia for median sternotomy. The application difficulties and complication risks of such methods limit their preference for postoperative analgesia as well. In addition, considering the pain caused by the drains in the thoracic wall after cardiac surgery, a method that can provide analgesia not only in the sternum area but also in the thoracic wall would be more fitting. In this respect, the ESP block is more advantageous due to its multidermatomal analgesia in the anterior and posterior areas of the thoracic wall, its easy application, and its low complication risk; also, the ESP block has been the fascial plane block that has been most studied in the last 3-4 years (6,7).

ESP block has been used safely by many authors for postoperative pain in thorax, abdomen, extremity, and spinal surgeries (6). However, there are a limited number of prospective randomized controlled trials for cardiac surgeries (7,12-14). Krishna et al. (13) applied bilateral ESP block for patients undergoing open heart surgery by administering 20 ml of 0.375% ropivacaine to each side under USG guidance, and similar to our study, they found a significant decrease in postoperative pain levels, opioid analgesic consumption, extubation duration, and ICU length of stay. Macaire et al. (12) also compared the patient group that did not undergo block operation in cardiac surgery with the patient group that underwent continuous ESP using 0.2% ropivacaine, and they reported that there was a significant reduction in postoperative morphine consumption and mobilization durations. In our study, we also found that the time from the operation to the first mobilization was statistically significantly shorter for the ESP group in the postoperative period. The difference between the two groups was almost 9 hours.

It has been known for a long time that the use of TEA for patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmia and respiratory complications (15). However, the most important concern for the use of TEA is that anticoagulant treatments used perioperatively in cardiac surgery facilitate epidural hematoma formation and cause the risk of neurological damage. Nagaraja et al. (7) applied continuous bilateral ESP block with 0.125% bupivacaine to one group and continuous TEA to another group for postoperative analgesia; they reported that ESP block had similar analgesic effectiveness with TEA and no complications were observed. Some authors have reported that ESP block can be safely applied even in cases where TEA cannot be performed due to thrombocytopenia, anticoagulant therapy, or coagulopathy (16-19). However, the data presented in these reports are quite limited and lack sufficient level of evidence. Therefore, more comprehensive randomized controlled trials are needed to determine the safety and effectiveness of this operation for such patient populations. No significant complications such as hematoma, neurological damage, infection, arrhythmia caused by local anesthesia, or pneumothorax were recorded in our study. In the literature, there are only 2 cases that are reported to have development of pneumothorax associated with ESP block (20,21).

Another method that is effective in postoperative pain control is the IV administration of narcotics with patient-controlled analgesia. However, it is recommended to reduce the use of narcotics within the scope of ERAS protocols due to the adverse effects of narcotic agents such as excessive sedation, ileus, constipation, severe nausea-vomiting, respiratory depression. In our study, IV PCA and morphine were used as rescue analgesia. In the ESP block group, 24-hour cumulative morphine consumption was observed to be reduced by at least 65%, similar to the study of Athar et al. (14). Along with the decrease in morphine consumption, the incidence of nausea and vomiting was also found to be significantly lower for the ESP group. In addition, it was determined that the duration before the first rescue analgesia use was significantly longer for the ESP group compared to the control group. These results are also consistent with the meta-analysis study of Huang et al. (22) with 590 patients about ESP block.

Few authors reported that sufficient parasternal analgesia did not occur during ESP block operation (23). Since the sensory prick test could not be performed in our study, we could not obtain information about the dermatomal analgesia level of our cases. On the other hand, some studies involving 3D imaging suggested that the local anesthetic solution injected in the ESP block spreads towards the epidural and neural foraminal spaces (24). Anatomically, this indicates that the ESP block should provide sternal analgesia. Further studies are required to clarify this paradoxical result.

The results of this study can be evaluated within some limitations. First, no evaluation for a period longer than postoperative 24 hours could be made since the ESP block was performed as a single shot. The second limitation is that the sensory prick test could not be performed, and dermatomal spread could not be evaluated because the patients received general anesthesia immediately after the ESP block was applied, and some patients were intubated and followed under sedation for about 6 hours in the ICU.

CONCLUSION

In our study, it was determined that ESP block applied bilaterally in adult cardiac surgeries decreased postoperative pain scores and morphine consumption. In addition, it was observed that the follow-up times of the patients in MV, their length of stay in the ICU and the duration before first mobilization were shortened. USG-guided ESP block is a safe application because its sonoanatomy is easily recognizable and it is far from risky anatomical structures, and also, its chance of failure is low. For these reasons, we think that ESP block should be included in the perioperative analgesic plan for cardiac surgery patients..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Hamidiye Clinical Research Ethics Committee (Date: 27.02.2020, Decision No: 2020.02.27-17).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Pancreatic cancer treatment after FOLFIRINOX: prognostic importance of chemotherapy dose intensity and albumin/globulin ratio in second line

Özgen Ahmet Yıldırım[1], Erkan Erdur[2]

[1]University of Health Sciences, Dr. Abdurrahman Yurtarslan Ankara Oncology Training and Research Hospital, Deparment of Medical Oncology, Ankara, Turkey
[2]University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Department of Internal Medicine, Division of Medical Oncology, Diyarbakır, Turkey

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ABSTRACT

Aim: Pancreatic adenocarcinoma (PA) is the seventh most common cause of cancer-related mortality. Our primary endpoint of study was to determine the relationship between albumin/globulin ratio (AGR) and progression-free and overall survival (PFS and OS) in second-line treatment after FOLFIRINOX. Our secondary endpoint was to assess treatment side effects and the relationship of treatment dose intensity with treatment type and AGR.

Material and Method: PA patients who followed-up between January 2014 and January 2021 were evaluated retrospectively. Age, gender, ECOG score and AGR recorded at the beginning of the second-line treatment. Thrombocytopenia, neutropenia, chemotherapy type, chemotherapy dose intensity, PFS and OS were recorded during the second-line treatment.

Results: Median age 64 (44-80), 72 (70.6%) male, 102 metastatic PA patients were evaluated. 76 (74.5%) patients were ECOG 0-1, 26 (25.5%) patients were ECOG 2. Of these patients in the second step, 68 (66.7%) received single-agent gemcitabine and 34 (33.3%) received Nab-paclitaxel + gemcitabine treatment. Progression and exitus events occurred in all cases. Median PFS was 166.8 days in the AGR>1.2 group, it was 80.7 days in the AGR<1.2 group (p=0.003). While the median OS was 295.7 days in the AGR>1.2 group, it was 144 days in the AGR<1.2 group (p=0.041). Dose intensity was 80.7% in the AGR>1.2 group, it was 71.3% in the AGR<1.2 group (p=0.002).

Conclusion: Even with palliative and advanced treatment, achieving a dose density close to 80% is a good prognostic indicator. AGR is a prognostic marker that remains effective in advanced stages of PA.

Keywords: Pancreatic cancer, dose intensity, albumin globulin ratio

INTRODUCTION

Pancreatic adenocarcinoma (PA) is the seventh most common cause of cancer-related mortality. It is observed in Europe, North America and Oceania, with the highest incidence at 7-10/10000 levels. Globocan data predicts that the incidence will double in 2040 (1). Incidence and mortality increases with age and peak just above 70 years of age. PA has poor prognosis, due to its asymptomatic early-stage clinical course and the weak systemic treatment efficacy compared to many other cancer types (2). Smoking, diabetes, obesity, advanced age, ethnic and genetic factors, Helicobacter pylori infection, non-0 blood type and chronic pancreatitis are the main risk factors. PA is mostly associated with environmental factors. PA constitutes 95% of pancreatic cancers (3). PA is a difficult cancer to diagnose at an early stage. Jaundice, pain, acholic stools, and signs of fatigue often accompany advanced disease. 85% of the cases are diagnosed in the locally advanced or metastatic stage and shows a very low 5-year survival rate (4). The rate of familial and genetically transmitted diseases is low. Among germline mutations, ATM, BRCA1, BRCA2, CDKN2A, PALB2, PRSS1, STK11, TP53, and Lynch syndrome related mismatch repair defects have been shown (5).

The treatment approach should be multimodal. FOLFIRINOX is the most effective treatment regimen based on available data, following surgery in resectable disease. In totally resected cases, a 3-year survival of over 60% can be achieved with adjuvant FOLFIRINOX regimen. However, FOLFIRINOX is not a regimen that

Corresponding Author: Özgen Ahmet Yıldırım, ozgenayildirim@gmail.com
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can be tolerated by all patients. The therapeutic benefit of single agent gemcitabine therapy is well established. It has been found that neoadjuvant FOLFIRINOX treatment increases the chance of resectability in borderline resectable cases (6-8).

Progression-free survival (PFS) and overall survival (OS) superiority of FOLFIRINOX to single-agent Gemcitabine has also been demonstrated in metastatic disease. Similarly, the combination of Nab-paclitaxel with gemcitabine has shown superior results to the single agent gemcitabine. Toxicity was observed more frequently in combination regimens and more frequent dose reductions were required (9,10).

Contrary to first-line therapy, comparative studies of second-line therapeutic approaches in PA are limited. Almost all patients who receive potent and toxic combined regimens such as FOLFIRINOX in the first line, receive single-agent therapy in the second line. At this stage, a limited number of patients can tolerate the combination of Nab-paclitaxel + gemcitabine (11). OS benefit was demonstrated in the NAPOLI-1 study, in which the combination of nanoliposomal irinotecan and fluorouracil was evaluated as a second step in cases who received a gemcitabine-based combined regimen in the first step. The association of this benefit with the general quality of life benefit has also been demonstrated (12,13).

Dose density is a parameter with well-proven prognostic value. In a study evaluating the relationship between dose intensity of FOLFIRINOX treatment and survival in pancreatic and other gastrointestinal cancers; relative dose intensity cut-off of 77-79% was found to be significant in terms of PFS and OS results (14).

Albumin and globulin are the main protein components of human serum. Albumin has been shown to be a prognostic marker in many cancer types, both showing the nutritional status and being a negative acute phase reactant (15). Globulin plays a critical role in immunity and inflammation with its cortisol-binding function (16). The relationship between albumin globulin ratio (AGR) and cancer prognosis are still a controversial issue in the literature. A meta-analysis published in 2018 found an association between low pretreatment AGR and low OS and PFS in many cancer types. (17).

In order to show that AGR is a practical and an inexpensive tool in terms of predictive prognostic value and treatment planning, we aimed to evaluate its relationship with chemotherapy dose intensity, which is a well-proven prognostic predictor.

In our study, we aimed to evaluate the second-line cases after FOLFIRINOX in metastatic pancreatic cancer, to discuss clinical and laboratory data and treatment results, retrospectively. At this point, our primary endpoint is to determine the relationship of patients' AGR with PFS and OS. Our secondary endpoint is to assess treatment side effects and the relationship of treatment dose intensity with treatment type and AGR.

MATERIAL AND METHOD

Within the scope of ethics committee approval for retrospective studies, approval was obtained from the Ethics Committee of Health Sciences University Gazi Yaşargil Training and Research Hospital (Date: 08.10.2021, Decision No: 896). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with a diagnosis of PA followed-up in the Medical Oncology Department of Gazi Yaşargil Training and Research Hospital between January 2014 and January 2021 were evaluated retrospectively. Inclusion criterias; being between the ages of 18 and 70, being inoperable at diagnosis and not suitable for local treatments, having completed FOLFIRINOX chemotherapy in the first line therapy, relapsed within the first 1 year after the end of the 12 cycles of FOLFIRINOX treatment and applied second-line treatment, and being able to receive second-line treatment for at least 3 months.

For the FOLFIRINOX regimen, standard oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2, and fluorouracil 400 mg/m2 IV push followed by 2400 mg/m2 46-hour continuous IV infusion chemotherapy every 14 days was considered. The standard 1000 mg/m2 1-8-15/28-day regimen was accepted for the gemcitabine regimen. The nab-paclitaxel regimen was accepted as 125 mg/m2 in combination with the gemcitabine standard regimen for 1-8-15/28 days.

The parameters of the patients were evaluated retrospectively; including age, gender, initial ECOG score, initial AGR, thrombocytopenia, neutropenia, chemotherapy type, chemotherapy dose intensity (%),PFS (days), and OS (days).

Patients were divided into two strata for AGR, ≥1.2 and <1.2. The parameters of these two layers were analyzed comparatively. AGR was calculated by; serum albumin/(serum total protein - serum albumin).

Chemotherapy dose intensity calculation was accepted as 100% in patients who were able to receive full dose in all sessions of chemotherapy administered in the first 3 months of the second line chemotherapy. In those who received missing session treatment due to delayed treatments in the first 3 months, the dose of that missing session was included in the dose intensity calculation

as 0%. Treatments after 3 months were not included in the dose intensity calculation, as it was concluded that the dose intensity-prognosis relationship could not be evaluated properly due to variable delays in the treatments after the first 3 months.

Patients with total bilirubin >3, presence of biliary stent, >3 ECOG score, creatinine levels above 1.4, presence of clinical conditions or complications that would interfere with oral feeding, presence of brain metastasis, and uncontrollable pain were excluded.

SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of the variables. The conformity of univariate data to normal distribution was evaluated with the Shapiro-Wilk francia test, while homogeneity of variance was evaluated with the Levene test. In the comparison of two independent groups according to quantitative data, the Independent-Samples T test was used together with the Bootstrap results, while the Mann-Whitney U test was used together with the Monte Carlo results. In the comparison of categorical variables with each other, Fisher Exact test exact results and Fisher-Freeman-Holton test was tested with Monte Carlo Simulation technique. Quantitative variables are mean±SD in tables. (standard deviation) and Median (Percentile 25%/Percentile 75%), while categorical variables were shown as n (%). Variables were analyzed at 95% confidence level, and p value less than 0.05 was considered significant.

RESULTS

Our study included 102 metastatic PA patients with a median age of 64 (44-80), 72 (70.6%) men, who met the criteria. All patients progressed between 3-12 months after completion of 12 cycles of FOLFIRINOX chemotherapy. 76 (74.5%) patients were ECOG 0-1, 26 (25.5%) patients were ECOG 2. Of these patients in the second line, 68 (66.7%) received single-agent gemcitabine and 34 (33.3%) received Nab-paclitaxel + gemcitabine (**Table 1**).

Table 1. Clinical, laboratory and demographic characteristics of the patients

Features	
Age (median, min-max)	64 (44-80)
Gender (female, n,%)	30 (29.4%)
Ecog	
0-1 (n,%)	76 (74.5%)
2+ (n,%)	26 (25.5%)
Chemotherapy	
Gemsitabin (n,%)	68 (66.7%)
Gemsitabin+nabpaklitaxel (n,%)	34 (33.3%)

Comparative analysis of PFS and OS results in AGR >1.2 and AGR<1.2 groups of all cases with progression and exitus events was performed. Median PFS was 166.8 days in the AGR>1.2 group, it was 80.7 days in the AGR<1.2 group (p=0.003). Median OS was 295.7 days in the AGR>1.2 group, it was 144 days in the AGR<1.2 group (p=0.041).

When we look at the chemotherapy dose density analysis with AGR; in both gemcitabine and gemcitabine-nabpaclitaxel groups, it was observed that the AGR value above 1.2 was higher than the patients with AGR below 1.2 (p<0.001). Dose intensities in AGR>1.2 and <1.2 groups were analyzed comparatively. While the dose intensity was 80.7% in the AGR>1.2 group, it was 71.3% in the AGR<1.2 group (p=0.002). Dose intensity analysis was performed according to chemotherapy type. While the dose intensity was found to be 73.2 in the group receiving single-agent gemcitabine, it was found to be 79.6 in the nab-paclitaxel gemcitabine group and the difference was not statistically significant (p=0.07). In the gemcitabine group; dose intensity was 71.1 in the AGR<1.2 subgroup, and was 80.6 in the AGR>1.2 group (p=0.0019). In the gemcitabine nabpaklitaxel combination group; dose intensity was 73.5 in the AGR<1.2 subgroup, and was 80.8 in the AGR>1.2 group (p=0.0028) (**Table 2**). No statistically significant correlation was found between AGR and documented myelotoxidity (**Table 3**).

Table 2. Relationship between dose intensity and albumin to globulin ratio (AGR)

	Gemsitabin	**Gemsitabin-nabpaklitaxel**	**All patients**
AGR	dose intensity (mean/median min-max)	dose intensity (mean/median min-max)	dose intensity (mean/median min-max)
<1.2	71.17/72 (66-76)	73.5/73 (72-76)	71.3/71 (66-76)
>1.2	80.60/80 (74-90)	80.8/81 (76-88)	80.7/ 80 (74-90)
p value	0.0019	0.0028	0.002

Table 3. Relationship between albumin to globulin ratio (AGR), myelotoxicity

Myelotoxicity	**AGR <1.2**	**AGR >1.2**	**p value**
Trombocytopenia			0.077
Grad 1-2 (n, %)	35 (61.4)	35 (77.8)	
Grad 3+ (n, %)	22 (38.6)	10 (22.2)	
Neutropenia			0.296
Grad 1-3 (n, %)	27 (47.4)	26 (57.8)	
Grad 4 (n, %)	30 (52.6)	19 (42.2)	

DISCUSSION

In our knowledge, our study is the first in the literature that evaluate the relationship between AGR and chemotherapy dose intensity. The data we have obtained may shed light on the predetermination of treatment tolerability in advanced line chemotherapy patients.

The first-line therapy in the treatment of metastatic PA is the primary therapy on which the clinician focuses his expectation. Generally, in the first-line treatment, it is fought within the framework of the longest possible PFS and quality of life goal. In cases that have received combination regimens such as FOLFIRINOX and progressed early, second-line treatment planning brings a pessimistic view for the clinician. In most cases, second-line treatment focuses on symptom palliation and promoting quality of life within the short pre-terminal PFS. In previous studies in this context, the superiority of gemcitabine nabpaclitaxel combination over single-agent treatments is clear in patients with good tolerance after the first step (18). It is clear that practical prognostic markers are needed to identify palliative targets in this poorly prognostic entity.

While evaluating the second-line therapeutic factors in our study, the data of the first 3 months of the treatment were discussed. Performing a retrospective study in advanced treatment is not healthy because of patient-based prognosis and poor prognosis of PA. Therefore, we evaluated prognostic factors, such as dose intensity and inflammatory parameters based on the first 3 months period.

Although chemotherapy dose intensity is an element that is tried not to be compromised in adjuvant treatments, the prognostic benefit of providing optimal dose density for metastatic cases is clear. However, optimal dose density may cause fatal complications in patients with low bone marrow reserve (19). At this point, the clinician should not forget that the main goal of advanced chemotherapy is palliation and quality of life support.

In pancreatic cancer, together with more studied inflammatory markers, such as neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR); low AGR levels has been shown to be poor prognostic for OS (20). In a recent study evaluating inflammatory parameters in pancreatic cancer, NLR and PLR were evaluated together. Both parameters were found to be an independent prognostic for OS (21). Since exitus and progression events occurred in all of the cases in our study, we performed our statistical evaluation directly on absolute PFS and OS data and found that AGR 1.2 level had a prognostic value. Tezuka et al. (22) evaluated AGR after neoadjuvant chemotherapy in borderline resectable pancreatic cancer, low AGR rate was associated with low OS. In a study investigating neoadjuvant chemotherapy in upper tract urethelial carcinomas, it was found that pre-treatment AGR level had no effect on long-term outcomes (23). However, the AGR level evaluated in this study belongs to chemotherapy-naive patients. In our study, AGR level was recorded before the second line, after FOLFIRINOX therapy. Therefore, in our study, we could achieve information about the metabolic reserve status after treatment.

There are additional poor prognostic factors that may affect the albumin level in pancreatic cancer. Biliary stasis and inflammation, which occurs while bilirubin levels are high, especially in the presence of occlusive icterus, decrease the level of albumin, which is a negative acute phase reactant. However, in a study conducted by Feng et al. (24) in 2018, it was concluded that pre-treatment bilirubin and albumin levels alone are not prognostic in advanced pancreatic cancer. However, the AGR rate is a relatively specific marker in the inflammation-synthesis cascade. Liu et al. (25) determined that AGR measured before treatment is an independent prognostic factor in metastatic gastric cancer. We emphasize that the prognostic correlation of these types of markers may increase in metastatic and advanced stage PA where catabolic processes are dominant.

The main limitation of our study is its retrospective design. Performing studies evaluating therapeutic results with a prospective method will provide stronger results. Stronger reference results can be obtained with a multicenter, multi-geographic study with a higher number of patients. Additional stratification of PFS results of first-line therapy may be beneficial in terms of reaching more reliable results.

CONCLUSION

As a result, advanced line treatment for this entity with a poor prognosis generally does not follow a satisfactory course. Even in palliative and advanced treatment, achieving a dose intensity close to 80% is a good prognostic indicator. AGR is a prognostic marker that remains effective in advanced stages of PA.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Health Sciences University Gazi Yaşargil Training and Research Hospital (Date: 08.10.2021, Decision No: 896).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Comparison of low-dose contrast computed tomography angiography findings with surgical results in living kidney donors

Hasan Gündoğdu[1], Sibel Aydın Aksu[2], V. Melih Kara[3]

[1]Recep Tayyip Erdogan University Faculty of Medicine, Department of Radiology, Rize, Turkey
[2]Health Sciences University, Haydarpaşa Numune Health Practice Center, Radiology Clinic, İstanbul, Turkey
[3]Başakşehir Çam and Sakura City Hospital, Department of General Surgery, İstanbul, Turkey

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ABSTRACT

Aim: To analyze the image quality and diagnostic performance of CT angiography using low dose (60 ml) contrast medium for living kidney donors and compare with surgical results.

Material and Method: Angiographic findings of 81 renal donor *Candida*tes in 128-slice MDCT were evaluated by two independent radiologists in terms of renal artery number, early bifurcation, renal vein variations, pelvicalyceal system and ureter variations. Results were compared with intraoperative findings. The image quality, diagnostic performance and interobserver agreement of MDCT obtained with low dose contrast material were analyzed.

Results: The mean age of the 81 living kidney donors included in the study was 49±12 (24-68) years. Left nephrectomy was performed in 71% (n=64) and right nephrectomy in 29% (n=17) of the donors. Intraoperative accessory arteries were detected in 22.2% (n:18) of the donors. The specificity, sensitivity, and accuracy for detecting accessory artery variation in MDCT were 100%, 88.9%, and 97.5%, respectively. Early bifurcation was observed in 21% (n=17) of the donors. Specificity, sensitivity and accuracy for early bifurcation detection were 98.4%, 94.1% and 97.5%, respectively. Renal vein variation was detected in 12.3% (n=10) of the donors. Specificity, sensitivity, and accuracy for renal vein variation detection were 100%. Variations of the pelvicalyceal system and ureter were observed in 3.7% (n=3) of the donors. The specificity, sensitivity, and accuracy for detecting pelvicalyceal system and ureteral variations were 100%. Interobserver agreement was excellent in detecting variations of accessory arteries, renal venous anomalies, pelvicalyceal system and ureters by MDCT (kappa: 1,000; p< 0.001). It was higher in early bifurcation detection (kappa: 0.853; p< 0.001).

Conclusion: MDCT angiography with a lower dose of iodine contrast at 60 mL in kidney donors is sufficient to detect vascular anomalies and provide anatomical information. It is possible to reduce the contrast agent dose in CTA without affecting the preoperative evaluation.

Keywords: Multidetector computed tomography, kidney, transplantation, contrast dose, contrast dose reduction

INTRODUCTION

Transplantation from a living donor is the most effective treatment option in patients with end-stage renal disease (1). In transplantation operations performed from living donors, preoperative evaluation and removal of the organ to be transplanted in a way that causes minimal damage to the donor and the organ itself is of great importance (2).

Clinical evaluation, laboratory tests and a comprehensive radiological study are necessary to determine the quality of the graft organ, to prevent future problems in the donor, to increase the success of the operation and to ensure that the graft works well in the recipient (3,4).

Detailed pre-operative knowledge of the donor's renal anatomy helps to minimize the risks of intraoperative bleeding, vascular or ureteral injury (5,6).

In the past, living kidney donors were subjected to preoperative evaluation with excretory urography and renal catheter angiography. However, because angiography is an invasive procedure and its value is limited in the detailed evaluation of renal venous anomalies, cross-sectional examination methods have taken its place (7).

Corresponding Author: Hasan Gündoğdu, drhasangundogdu@gmail.com
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The vascular and pelvicalyceal anatomy of the donor can be identified by CT or MRI (8).

With the introduction of multi detector computed tomography (MDCT), increased scanning speed, higher spatial resolution, thinner sections and superior image quality have been achieved. CT has become a safe and widely accepted method for the preoperative evaluation of the renal vasculature, due to the higher spatial resolution, acquisition rate, and greater ability to detect small accessory arteries than MRI (9,10).

The use of high-dose contrast media in computed tomography can cause acute kidney injury (CI-AKI), known as contrast-induced nephropathy not associated with another nephrotoxic event, when there is a sudden increase in serum creatinine after exposure to iodinated contrast media. This condition is normally self-limiting, but can lead to increased morbidity and mortality (11,12).

The degree of renal artery opacification defines the technical adequacy of CT Angiography (CTA) scanning and is proportional to the rate and dose of contrast agent administration. Recent advances in CT technology and faster image acquisition times can shorten the time required for opacification of the vascular system. Therefore, it makes it possible to reduce the contrast agent dose used in CTA (13).

Due to the difficulty of finding renal donors, the contrast agent dose to be applied to the kidney to be transplanted is important. It has been reported in the literature that 75-120 ml of contrast material is used in preoperative CT angiography in renal donors (14-16).

The use of less contrast reduces the risk of potential complications associated with an iodinated contrast agent, such as an allergic reaction or nephrotoxicity. Therefore, the contrast dose should be reduced to the lowest dose that will not affect the imaging quality (13).

The aim of this study is to analyze the image quality and diagnostic performance of CTA using 60 ml of contrast medium for living kidney donors and compare it with surgical results.

MATERIAL AND METHOD

The study was reviewed and applied by Non-Interventional Clinical Researchs Ethics Committee of Health Sciences University, Haydarpaşa Numune Training and Research Hospital Health Application Center (Date: 02.08.2021, Decision No: 2021/197-3396). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Between February 2015 and April 2021, 110 potential living donors who underwent CTA imaging before renal transplantation in our hospital were retrospectively reviewed. Nineteen patients were excluded from the study because nephrectomy was not performed due to malignancy and/or positive cross-match results, and 10 patients were excluded because the contrast medium rate (3.5 ml/sec) was different. 81 patients were included in the study.

CTA imaging in renal donors was performed with 128-slice CT (Optima CT 660, Logic Healthcare, Waukesha, USA) with 120 Kv radiation dose, 150 mA, tube output between 200-400, 0.6 pitch, 0.4 sec rotation time, 0.625 mm slice thickness and It was done with 40 mm collimation.

The patients were taken to the to the CT scan as fasting for at least 6 hours and drinking 250-500 cc of water in the last half hour. The CTA procedure and breathing instructions were explained to each patient.

60 ml of contrast material (iohexol, Omnipaque 350, Amersham Health, Princeton, NJ) was given to the patients through an 18 G cannula with an automatic injector (Ulrich Inject CT Motion, Ulrich Medical, Buchbrunnenweg, Germany) at a rate of 4 ml/sec. After the contrast application, 40 cc of saline was administered at the same rate.

Imaging was performed by taking arterial (25 sec), portal (60 sec) and late venous (300 sec) phases in the craniocaudal direction. Scanning area starting from the top of the diaphragm domes; It was determined to be just below the common iliac arteries in the arterial and venous phase, and up to the symphysis pubis in the late venous phase.

All acquired images were transferred to the workstation (Advanced Workstation, GE Healthcare, Milwaukee, WI, USA) for postprocessing.

Two experienced independent radiologists (S.A and H.G.) reviewed images from each CT scan at the workstation preoperatively. Image analyzes were performed without knowledge of other reviewers or surgical results.

Multiplane remodeling (MPR) and volume rendering (VR) techniques were generally used for 3D CT angiography. However, the maximum intensity projection (MIP) technique was used especially when needed for small vessels.

Renal artery anatomy was evaluated in arterial phase, venous anatomy was evaluated in arterial and/or portal phase, and collecting system anatomy and variations were evaluated in late venous phase.

Both radiologists recorded the number of renal arteries. Any branch within 2.0 cm of the aorta was classified as

early branching. Other associated findings, including stenosis and aneurysms, were recorded for each artery. Renal vein anatomy was evaluated for the presence of retroaortic and circumaortic veins. Pelvicalyceal system and ureteral anomalies were recorded.

None of the patients developed complications related to contrast material. In addition, there was no patient who could not be evaluated due to poor image quality or insufficiency.

Donor nephrectomy was performed between 4 weeks and 6 months (mean 3 months) after CT examination. Transplant surgeons recorded the side of the nephrectomy kidney, the number of renal arteries, the presence of early branching arteries, the presence of renal vein anomalies, pelvicalyceal system and ureter anomalies.

Statistical Analysis

Statistical analyzes were performed with IBM SPSS Statistics, Version 23.0 (SPSS Inc., Chicago, USA) and MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Categorical data of both groups were reported as frequencies and percentages within the groups (n, %). The relationship between observers and surgery was assessed by kappa concordance analyses. In addition, the diagnostic performance of the observers according to surgery was evaluated and reported as % sensitivity and % specificity. The limit of significance was accepted as $p < 0.05$.

RESULTS

The mean age of 81 living kidney donors included in the study was 49±12 (min-max:24-68) years; 51.9 % (n=42) were female and 48.1% (n=39) were men. Left nephrectomy was performed in 71% (n=64) and right nephrectomy in 29% (n=17) donors (**Table 1**).

Intraoperative accessory renal artery was observed in 22.2% (n:18) of the donors; single renal artery in 77.8% (n=63), double renal artery in 19.8% (n=16), and triple renal artery in 2.4% (n=2). Specificity, sensitivity, and accuracy for accessory artery detection in CTA for observer 1 and observer 2 were 88.9%, 100%, and 97.5%, respectively (16/18). Excellent agreement among observers was detected (kappa: 1.00; p< 0.001) (**Table 2**). More than three renal arteries were not detected in any donor. Both observers evaluated the presence of triple renal artery as bilateral renal artery in two donors. Retrospectively, these arteries were identified as superior and inferior polar arteries with a diameter of less than 2 mm, respectively. These arteries were not considered important by the surgeon.

Early bifurcation was detected in 21% (n=17) of the donors. Specificity, sensitivity, and accuracy for early bifurcation detection in CTA for observer 1 and observer 2 were 98.4%, 94.1%, and 97.5%, respectively (16/17). High agreement among observers was detected (kappa: 0.853; p< 0.001) (**Table 3**). The mean length from aorta to renal artery branching was 21.2 mm in the two donors in which early branching was misregistered, possibly confused with early branching.

Renal vein anomaly was observed in 12.3% (n=10) of the donors, and all of them were in the left kidney. Specificity, sensitivity, and accuracy for detecting renal vein variation in CTA for observer 1 and observer 2 were 100. Excellent agreement was found between observers (kappa: 1,000; p< 0.001). Of the donors with renal vein anomalies, 80% (n:8) had a retroaortic and 20% (n:2) had a circumaortic renal vein. All of the variations were detected by both observers.

A normal single ureter was detected in 78 of 81 intraoperative kidneys. Variations of the pelvicalyceal system and ureter were observed in 3.7% (n=3) of the donors. There was one partial ureteral duplication in the right kidney and two complete ureteral duplications in the left kidney. Specificity, sensitivity, and accuracy for detecting renal pelvis and ureter variations on CT for observer 1 and observer 2 were 100% (3/3). Excellent agreement was found between observers (kappa: 1,00; p<0.001).

Table 1. Demographic characteristics of the renal donors

	n (%)/Mean ±SD
Sex	
Female	42 (51.9)
Male	39 (48.1)
Age (years)	49±12
Side	
Left	64 (79)
Right	17 (21)

Table 2. Sensitivity, specificity, and accuracy of multidetector CT angiography for presence of accessory arteries

	Sensitivite %	Spesifite %	Accuracy (%)	Kappa	P
Observer 1	88.9 (16/18)	100 (63/63)	97.5	1	<0.001
Observer 2	88.9 (16/18)	100 (63/63)	97.5	1	<0.001

Table 3. Sensitivity. specificity. and accuracy of multidetector CT angiography for presence of early branching of renal arteries

	Sensitivite %	Spesifite %	Accuracy (%)	Kappa	P
Observer 1	94.1 (16/17)	98.4 (63/64)	97.5	0.853	<0.001
Observer 2	94.1 (16/17)	98.4 (63/64)	97.5	0.853	<0.001

DISCUSSION

Kidney transplantation remains the most effective treatment option for patients with end-stage renal disease. Transplantation can be done from cadavers or from living kidney donors. According to recent data, living donor transplants account for more than two-thirds of all kidney transplants performed in Turkey, compared to only about a quarter in the United States (17,18).

Donor safety is the primary goal of living donor transplant programs. All potential donors should have standard laboratory tests, clinical evaluation prior to kidney transplant surgery, and anatomical evaluation of the kidney and renal vessels should include imaging studies (19,20).

The number, length, location and branching pattern of the renal arteries, venous anomaly, kidney and collecting system should be evaluated preoperatively by imaging methods (21).

Multi-detector CT angiography (MDCTA), contrast-enhanced MR angiography and digital subtraction angiography (DSA) can be applied in the structural evaluation of the kidney and renal vascular system in living kidney donors. However, the use of DSA has decreased because it is invasive and does not provide detailed information about venous anatomy and renal parenchyma. MR imaging is not sensitive in detecting urolithiasis and its spatial resolution is lower than MDCTA (10,22).

MDCT is a non-invasive, easily accessible and relatively inexpensive imaging modality. In addition, MDCT is preferred to other imaging modalities due to its high spatial resolution, acquisition rate, ability to detect small accessory arteries, and more sensitive to identify and characterize vascular calcifications (23).

Adequate vascular augmentation is essential to obtain a high-quality angiogram. The degree of arterial opacification defines the technical proficiency of a CTA scan. It is proportional to the rate and dose of contrast agent administration (24).

The organ taken in donor surgeries is used in another individual and the donor continues his life with the remaining kidney. For this reason, it is of great importance to remove the organ to be transplanted in a way that causes the least damage to the donor and the organ.

CI-AKI is related to the amount of contrast material used, and although it is usually self-limiting, it can lead to increased morbidity and mortality (11). Groups of patients with hypertension, advanced age, and recent exposure to nephrotoxic drugs are at risk of developing CI-AKI. Therefore, the contrast dose should be kept to a minimum, provided it does not affect the overall quality of the image (12).

Recent advances in CT technology have allowed faster image acquisition times, reducing the time required to opacify the pulmonary vasculature. This made it possible to consider reducing the dose of contrast agent used in other angiographies as well as in CT pulmonary angiographies (13).

To the best of our knowledge, our study is the first study in which the diagnostic performance of CTA obtained using low-dose contrast material was compared with surgical results in renal donors. It is aimed to reduce the risk of complications and the cost of screening by reducing the dose, and to increase patient safety.

Although the contrast agent doses used in CTA imaging for kidney donors vary, they have decreased over the years with the development of CT technology. Rankin et al. (14) used 150 ml, Kawamoto et al. (25) used 120 ml, Ghonge et al. (26) used 100 ml of contrast agent for renal donors.

In our study, CTA had a diagnostic accuracy of 97.5% for number of arteries when compared with intraoperative findings. Similarly, Sarier et al. (2) reported an accuracy rate of 97.9% with CTA in their study on 2,144 living donors using an average of 90 ml of contrast. In our study, the specificity and sensitive values for accessory renal artery in CTA were 100% and 88.9%, respectively, and Sarıer et al. similar to his work.

When CTA and intraoperative findings were compared in terms of early bifurcation in our study, the specificity, sensitivity, and accuracy were 98.4%, 94.1%, and 97.5%, respectively. Kawamoto et al. (14) reported that early branching of the renal arteries could be detected with an average accuracy of 96% in his study by applying 100 ml of contrast material.

Çınar et al. (27) found the retroartic and circumaortic renal vein variation rate of 9.4% in their study on 504 living donors using 80-100 ml contrast. Holden et al. (28) found a 14% vein variation rate in 80 living donors. In the study, this rate was similar to that of Holden et al. We think that this is due to the fact that the number of patients in the study is less than that of Çınar et al., and that it is close to that of Holden et al. In the study, the specificity, sensitivity and accuracy in detecting renal vein variations in MDCT were similar to the study of Turkvatan et al. (15).

The rate of detection of pelvicalyceal system and ureters variation in our study was similar to the literature. The specificity and sensitivity of detection with MDCT was 100%, and it was similar to the study of Türkvatan et al. (15).

In the literature, some authors recommend scanning before contrast application to detect the presence of nephrolithiasis and urolithiasis, while others do not

(15,28,29). In our study, unhanced imaging was not performed in order to minimize the radiation dose received.

We experienced that nephro and urolithiasis can be detected in arterial phase images. In a literature study of 65 patients using MDCT, all five patients with urolithiasis were seen on both non-contrast and contrast-enhanced scans (30). In our study, we detected four donors, two with nephrolithiasis and two with urolithiasis, on arterial phase images.

The limitations of our study are that it is retrospective, single-centered, and the images were evaluated by only two observers. In addition, renal function tests and the incidence of CI-AKI were not compared with CTA with high-dose contrast material.

CONCLUSION

Our study showed that CTA performed with low-dose contrast agent (60 mL) on 128-slice CT in renal donors is clinically applicable without adversely affecting the image quality and diagnostic value, and provides sufficient preoperative information. New studies are needed to determine that CT with less slices provides sufficient preoperative information.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was reviewed and applied by Non-Interventional Clinical Research Ethics Committee of Health Sciences University, Haydarpaşa Numune Training and Research Hospital Health Application Center (Date: 02.08.2021, Decision No: 2021/197-3396).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Are scoring systems detecting acute appendicitis reliable? a prospective clinical study

Mustafa Taner Bostancı[1], İbrahim Yılmaz[1], Sanem Güler Cimen[1], Koray Kosmaz[2], Aysun Gökçe[3], Mehmet Alperen Avcı[4]

[1]University of Health Sciences, Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of General Surgery, Ankara, Turkey
[2]University of Health Sciences, Ankara Training and Research Hospital, Department of Surgery, Ankara, Turkey
[3]University of Health Sciences, Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Pathology, Ankara, Turkey
[4]Sorgun State Hospital, Department of General Surgery, Yozgat, Turkey

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ABSTRACT

Aim: The diagnosis of acute appendicitis is still challenging. Negative appendectomy rate is reported as 20-30%. Therefore, various scoring systems have been developed to prevent unnecessary appendectomies. The aim of our study is to analyze the diagnostic value of different scoring systems in acute appendicitis.

Material and Method: The study conducted with 200 consecutive patients who were operated with the diagnosis of acute appendicitis. After the admission and deciding the operation via experienced general surgeon, the probability of acute appendicitis was calculated using via 6 different scoring systems: Alvarado, Eskelinen, Ohmann, Lintula, RIPASA, Fenyo, respectively, and results were analyzed statistically. $p<0.05$ was considered statistically significant.

Results: RIPASA had the highest sensitivity (83.8%) and accuracy (78%) ratio in all patient groups; The Lintula scoring system had the highest specificity (66.7%). Sensitivity values were found to be higher in males, and the sensitivity of Lintula (44.6%/12.6%; p: 0.001) and Fenyo (67.6%/19.4%; $p<0.001$) scores were significantly higher in males. The spesificity value was significantly higher for Eskelinen (85.7%/35.7%; p: 0.031) and Lintula (100%/50%; p: 0.022) in females.

Conclusion: RIPASA is the scoring system with the highest sensitivity for both genders. Eskelinen and Lintula is noteworthy in females. We believe that the use of scoring tests with classifying according to gender may lead to a decrease in negative appendectomies.

Keywords: Acute appendicitis, scoring systems, appendectomy, clinical decision

INTRODUCTION

Acute appendicitis is one of the most common causes of abdominal pain in patients admitted to the emergency, and acute appendectomy operation is the major part of general surgery education (1). Diagnosis of acute appendicitis should be done as soon as possible to minimize morbidity, mortality and unnecessary surgical interventions. However, despite the improvements in the accuracy of diagnostic methods, the level of diagnostic failings reach 20-30% (2). The diagnosis depens on history, symptoms, physical examination, and laboratory findings. Routine radiological examinations are also used in the emergency department, especially in clinically ill-defined patients. However, radiological examinations are time-consuming methods and have not been found to be specific (3). These challenges in diagnosing acute appendicitis led researchers to develop some clinical scoring systems and consequently, many scoring systems have been described from the 1980s (4-8). In our study, we aimed to analyze the effectiveness of different scoring systems in the diagnosis of acute appendicitis in randomized patients hospitalized for appendectomy operation.

MATERIAL AND METHOD

This prospective study was conducted with 200 consecutive patients who underwent appendectomy with the diagnosis of acute appendicitis between November 2017 and June 2018, after the approval of Clinical Research Ethics Committee of Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 08.10.2021, Decision No: 896), and under circumstances of Helsinki Declaration of Principles.

Corresponding Author: Özgen Ahmet Yıldırım, ozgenayildirim@gmail.com
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Each patient was hospitalized after examination by one same general surgeon with a diagnosis of acute appendicitis, and detailed anamnesis, physical examination findings and laboratory tests results (complete blood count, biochemistry, urine test) were enrolled. Informed consent was obtained from all individual participants included in the study. Preoperative abdominal ultrasonography (USG) was performed to 169 patients, and abdominal computed tomography (CT) was performed to 98 patients. A questionnaire consisting of the parameters of the whole scoring systems included in the study was filled out according to the symptom and test results determined by the general surgery residents for each patient. Then the acute appendicitis probability was calculated according to six different scoring systems and the obtained scores were recorded. The cut-off points as described in the original report of each scoring system were used. The assumed Cut-Off (COP) points were 7 for Alvarado, 55 for Eskelinen, 12 for Ohmann, 21 for Lintula, 7.5 for RIPASA, and -2 for Fenyo (**Table 1**) (4-9).

The same general surgeon who decided to perform the operation did not know the results of the scoring before the operation. All of the pathologic materials were worked on and analyzed histopathologically and the results confirmed via the same pathologist after the operation. Neutrophilic infiltration of the appendiceal wall, mucosal ulceration, cryptitis, crypt abscesses, necrosis were determined as appendicitis histopathologically, and without each of these findings, cases were accepted as "disease absent category". Inclusion criterias were all patients with phlegmonous, gangrenous or perforated appendicitis, and had suspended or ill-defined clinics without age or gender limitation. All patients were informed about the study and written informed consent was obtained from them. Patients who did not consent the study or operation, used antibiotics and referred from another hospital to our hospital were excluded from study.

Statistical Analysis

The data were analyzed by the Statistical Package for Social Sciences 20.0 (SPSS). In order to determine the sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), accuracy values of scoring systems; a cross-table and the Mc Nemar test, Chi-square test were used. $p<0.05$ was considered statistically significant.

RESULTS

The mean age was 31 (19-88), and 162 patients (81%) were male. Pathology reports were found to be acute appendicitis in 179 patients, while the remaining 21 pathologic material were evaluated as innocent appendix. A negative appendectomy rate was 10.5%. Thirty-six of

Table1. Clinical parameters and cut-off points of the scoring tests

Clinical signs	Alvarado	Eskelinen	Ohman	Lintula	RİPASA	Fenyo
Age			+		+	
Gender				+	+	+
Duration of pain (<48sa)		+			+	+
Increase of pain level						+
Pain level				+		
Continuous pain			+			
Pain localized in right lower quadrant		+	+	+	+	
Migration of pain	+		+	+	+	+
Loss of appetite	+				+	
Nausea & vomiting	+			+	+	+
Difficulty in miction						
Increased pain when cough						+
Right lower quadrant tenderness	+	+			+	
Rigidity		+				+
Defense			+	+	+	
Rebound	+	+	+	+	+	+
Bowel sounds				+		
Rovsing's sign					+	
Fever (>37.3°c)	+			+	+	
Leucocyte (>10000)	+	+	+		+	+
Neutrophilia (>% 75)	+					
No dysuric symptoms			+			
Negative urine test					+	
Foreigner					+	
Cut-off	**7**	**55**	**12**	**21**	**7.5**	**-2**

the patients (18%) were undergone laparoscopic surgery, whereas the others (82%) were undergone conventional surgery. Sensitivity and specificity rates of the clinical parameters were summarized in **Table 2**. The comparison of scoring systems with the pathology results is shown in **Table 3**. The data obtained from the comparison of scoring systems for male and female genders are shown in **Table 4**, and **Table 5**. The sensitivity of Lintula (p=0.001) and Fenyo (p<0.001) scoring systems were significantly higher in males. The specificity of Eskelinen (p=0.031) and Lintula (p=0.022) scoring systems were significantly higher in females. We revealed that abdominal CT was superior to abdominal USG in terms of sensitivity (p<0.001), specificity (p=0.013) and accuracy rate (p<0.001) in the evaluation of the radiologically obtained data compared to histopathology results (**Table 6**).

Table 2. Comparison of clinical signs in terms of sensitivity, specificity, PPV*, NPVº

Clinical signs	Sensitivity	Specificity	PPV*	NPVº	Accuracy
Duration of pain (<48sa)	73.2	28.6	89.7	11.1	68.5
Increase of pain level	69.3	52.4	92.5	16.7	67.5
Pain level	58.7	33.3	88.2	8.6	56
Continuous pain	92.7	28.6	91.7	31.6	86
Pain localized in right lower quadrant	59.8	52.4	91.5	13.3	59
Loss of appetite	70.9	61.9	94.1	20.0	70
Nausea & vomiting	49.7	47.6	89.0	10.0	49.5
Difficulty in miction	9.5	100	100	11.5	19
Increased pain when cough	56.4	61.9	92.7	14.3	57
Right lower quadrant tenderness	98.3	0	89.3	0	88
Rigidity	35.2	66.7	90.0	10.8	38.5
Defense	64.2	38.1	89.8	11.1	61.5
Rebound	72.6	47.6	92.2	16.9	70
Bowel sounds	7.3	95.2	92.9	10.8	16.5
Rovsing's sign	17.3	81.0	88.6	10.3	24
Fever (>37.3˚c)	79.9	9.5	88.3	5.3	72.5
Leucocyte (>10000)	19.0	76.2	87.2	9.9	26
Neutrophilia (>% 75)	52.0	28.6	86.1	6.5	49.5
Negative urine test	78.2	19.0	89.2	9.3	72

PPV*=Positive predictive value, NPVº=Negative predictive value

Table 3. Comparison scoring tests in terms of sensitivity, specificity*, PPV, and NPVº

Scoring tests	Sensitivity	Specificity	PPV*	NPVº	Accuracy
Alvarado	67	61.9	93.8	18.1	66.5
Eskelinen	64.8	52.4	92.1	14.9	63.5
Ohmann	76.5	42.9	91.9	17.6	73
Lintula	39.1	66.7	90.9	11.4	42
Fenyo	59.2	57.1	92.2	14.1	59
RIPASA	83.8	28.6	90.9	17.1	78

PPV*=Positive predictive value, NPVº=Negative predictive value

Table 4. Comparison of sensitivity of scoring tests according to gender

		Sensitivity					
Gender	**n**	**Alvarado**	**Eskelinen**	**Ohmann**	**Lintula**	**Fenyo**	**RIPASA**
Male	162	68.9%	66.9%	77.7%	44.6%	67.6%	83.8%
Female	38	58.1%	54.8%	71.0%	12.9%	19.4%	83.9%
p		0.242	0.131	0.822	0.001	<0.001	0.99

Table 5. Comparison of specificity of scoring tests according to gender

		Specifity					
Gender	**n**	**Alvarado**	**Eskelinen**	**Ohmann**	**Lintula**	**Fenyo**	**RIPASA**
Male	162	57.1%	35.7%	28.6%	50.0%	42.9%	21.4%
Female	38	71.4%	85.7%	71.4%	100%	85.7%	42.9%
p		0.525	0.031	0.061	0.022	0.061	0.306

Table 6. Comparison of imaging methods with pathological results

Screening Tests	Sensitivity	Specificity	PPV*	NPVº	Accuracy
Abdominal USG	78.1	11.1	87.3	4.6	66.2
Abdominal CT	95.1	50	90.6	66.6	87.7
p	<0.001	0.013	0.444	<0.001	<0.001

USG=Ultrasonography, CT=Computed tomography, PPV*=Positive predictive value, NPVº=Negative predictive value

DISCUSSION

Acute appendicitis is the most common cause of abdominal pain in emergency clinics worldwide. As a matter of fact the imminent appendectomy prevents many complications, and the quick and accurate diagnosis of acute appendicitis must be performed in time (10). The fact that the clinical entity may show different clinical manifestations in early period and lack of a fully reliable diagnostic test may leave surgeons unstable in the diagnosis, and in addition this situation may lead them to perform unnecessary appendectomy operation for some cases.

To date, the most commonly used imaging modality for the diagnosis of acute appendicitis is abdominal USG. Although abdominal USG, abdominal CT and laparoscopy are used effectively in the diagnosis, the rate of negative appendectomy is 20-30% and the rate of non-diagnosed perforated appendicitis is 4% (11,12). It is known that the technical factors such as the experience of the radiologist who examined the diagnostic accuracy of abdominal USG and the quality of the device and the patient's factors such as body mass index, localization of the appendix, and density of intestinal gases affect the diagnostic accuracy of abdominal USG. A range of sensitivity and specificity varies 44-100%, 47-99%, respectively (13). Abdominal CT is a more reliable method for the diagnosis of acute appendicitis and it is reported that the sensitivity and specificity rates are 94%, 95%, respectively (14). However, abdominal CT have some disadvantages such as exposure to ionizing radiation, long preparation time and higher cost (15). Wani et al. (16) stated that the indiscriminate use of abdominal CT could cause ambiguous results especially in patients with early appendicitis and may lead to unnecessary appendectomy in patients with spontaneous regression. In our study, abdominal CT was superior to abdominal USG in terms of sensitivity, specificity and accuracy rates in the diagnosis of acute appendicitis correlated with the literature.

The pain that begins in the epigastric region and is located in the right lower quadrant is typical for acute appendicitis. In our study, patients who were admitted to the emergency department with right lower quadrant pain and were operated with a preliminary diagnosis of acute appendicitis were expected to have a high sensitivity in the "right lower quadrant tenderness" parameter when evaluated with histopathological findings. In addition, "acute continuous abdominal pain" parameter had high sensitivity value and the accuracy rate was remarkable. Moreover the parameters of "no difficulty in urination", "normoactive bowel sounds", and "positive Rovsing sign" showed high specificity values.

Consequently, the difficulties in diagnosing acute appendicitis led clinicians define various scoring systems in order to reduce the frequency of negative surgery. One of them, Alvarado score, is the first known for the diagnosis of acute appendicitis and is the most well known in the general surgery society. The score is calculated over 10 points and a score of ≥7 is considered to be an acute appendicitis marker. The sensitivity rates in the literature are reported to be 39-100% and the specificity rates are between 41-98% (17). Eskelinen score is developed to be more specific to female gender. When a score of ≥55 was determined as the cut off value, it was found that the sensitivity of 79% and the specificity of 85% in literature (5). The decimal value of the Eskelinen score is the disadvantage of its practical application (5). The Ohmann score was developed to reduce the number of negative appendectomies and ≥12 score was accepted as a marker of acute appendicitis. Ohmann stated that he reduced negative appendectomy rates to 2% (6). The Lintula score is another scoring system with a specificity of 87% of its sensitivity when it's score is ≥21 (98%) (7). The RIPASA score, which was defined in recent years, is another scoring system, and it is reported that sensitivity is 87%, and specifity is 67% when the score is ≥7.5 (8). It includes some parameters such as age, gender and duration of symptoms which are lack in the Alvarado score (8). Another scoring system, the Fenyo-Lindberg score, was reported to have a sensitivity of 73% and a sensitivity of 73% when the score is ≥-2 (9).

Almost all scoring systems concerning about diagnosis of appendicitis varies in different countries depending on the differing nutritional, working and cultural conditions. In our country, there are some studies about the accuracy of scoring systems in the diagnosis of acute appendicitis. Erdem et al. (12) found that the specificity of Ohmann and RIPASA tests was higher to the Alvarado and Eskelinen tests for the diagnosis of acute appendicitis in their study which is conducted with 113 patients. Kırkıl et al.(18) reported that the sensitivity of the Lintula test was higher than the Alvarado test in a study of 114 patients. Yılmaz et al. (19) reported that Alvarado test was more sensitive than Ohmann test in the diagnosis of acute appendicitis. Yoldas et al. (20) reported that, when evaluating the accuracy of the Lintula score in the diagnosis of acute appendicitis, it was an appropriate method for Turkish society.

Currently, the studies considering two or three scoring systems are quite common compared to studies checked more than three scoring system in the literature. Besides, it is accepted as highly valuable when the sensitivity and specificity values are above 80% (21). In our study, when we compared the results of frequently used six different scoring systems statistically, even its specificity was not

too high, the 83.8% sensitivity ratio obtained for RIPASA scoring system was remarkable. When we compared the scoring systems in terms of gender variable, different results were obtained. In fact, the sensitivity values of scoring systems were generally higher in males and also this difference was statistically significant for Fenyo, and Lintula in our study. When we analyzed in terms of specificity, the difference was statistically significant for Eskelinen, and Lintula which were higher in females compared to males. RIPASA was the scoring system with a sensitivity ratio of over 80% for both sexes according to the current study, and these findings were correlated with the literature (21).

We did not include possible appendicitis cases; our population is compromised of diagnosed appendicitis by general surgeon with clinical findings, physical examination, laboratory and imaging findings without scoring systems results. We could have missed some true negative and false negative data which could affect the NPV, PPV, sensitivity, specificity rates. We focused on only clinically diagnosed appendicitis cases.

CONCLUSION

RIPASA had the highest sensitivity for general population and the genders according to the study. Eskelinen and Lintula were noteworthy in females with high specificity values. Moreover, Fenyo and Lintula had considerably high sensitivity values in males. We concluded that the use of these tests in question with classifying distinctively according to gender may reduce the rate of negative appendectomy especially in females and in the patients not in the most common seen age group and may help clinicians in diagnosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Research Ethics Committee of Health Sciences University Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 08.10.2021, Decision No: 896).

Informed Consent: All patients signed the free and informed consent form.

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Original Article

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Basilar artery flow characteristics and color Doppler sonography findings in healthy infants

Hasibe Gökçe Çınar, Berna Uçan

University of Health Sciences, Dr. Sami Ulus Training and Research Hospital, Department of Pediatric Radiology, Ankara, Turkey

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ABSTRACT

Aim: Transcranial Doppler (TCD) is a widely used method for the evaluation of vertebrobasilar system. There is not neither a consensus nor significant number of publications about normal spectral Doppler waveform and resistance index (RI), peak systolic velocity (PSV), and end diastolic velocity (EDV) values of basilar artery (BA). We aim to define normal PSV, EDV, RI values of BA via TCD in healthy infants.

Material and Method: BA was evaluated from anterior fontanelle by creating sagittal and coronal images. Color Doppler ultrasonography (CDUS) and spectral Doppler examinations were performed by placing the cursor in the middle portion of BA. PSV, EDV, and RI values were recorded. Patients were divided into 4 subgroups to analyze the change of normal values according to age groups: (1) 0-120 days, (2) 121-180 days, (3) 181-270 days, (4) >271 days.

Results: 115 healthy infants were included into the study. A weak positive correlation was found between PSV, EDV values and age; meanwhile a weak but significant negative correlation was present between age and RI values. We cannot find any correlation between sex and CDUS parameters.

Conclusion: BA PSV, EDV and RI values change by age. No correlation is present between CDUS characteristics and sex. BA pathologies are rare in pediatric population, nevertheless knowing normal CDUS characteristics can help radiologists for an appropriate assessment.

Keywords: Basilar artery, blood flow, Doppler ultrasonography, transcranial Doppler ultrasound, infant

INTRODUCTION

Transcranial Doppler ultrasound or sonography (TCD) is main evaluation method of vertebrobasilar system and circle of Willis in pediatric patients before closing anterior and posterior fontanelles (1,2). Both color Doppler ultrasound (CDUS) and spectral Doppler examinations can be performed transcranially (3,4). Normal CDUS characteristics and spectral Doppler waveforms of many intracranial vascular structures such as common, internal/external carotid arteries, vertebral arteries and intracerebral arteries etc. were previously defined (5-7).

Basilar artery (BA) pathologies are not very common in infants. The main diagnosis in the pediatric population (between the ages of 0-17 years old) resulting from the basilary artery is mostly stroke. In these cases, the diagnosis was generally taken with computed tomographic angiography and/or conventional angiography (8-10). In literature, the knowledge about TCD usage for the evaluation of BA pathologies is very limited. In the same way, during our daily practice, we have noticed that a limited number of radiologists evaluate BA waveform during routine TCD. Also, as far as we know, there is not neither a consensus nor significant number of publications about normal spectral Doppler waveform and resistance index (RI), peak systolic velocity (PSV), and end diastolic velocity (EDV) values of BA.

Our study aims to define normal PSV, EDV, RI values of BA via TCD in healthy infants and contribute a limited information repository.

MATERIAL AND METHOD

This current prospective study was carried out with the permission of Keçiören Training and Research Hospital Ethics Committee (Date: 20.06.2018, Decision No: 2012-KAEK -11/2238). Informed consent form was signed by the parents of all participants. The study data was collected between February 2019 and August 2019.

Corresponding Author: Berna Uçan, drbernakahya@gmail.com

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We performed TCD for examining BA to the infants who were referred to pediatric radiology clinic for a transcranial ultrasound examination. They were all healthy children whose parents were willing to participate, or the children came for another health issues: such as developmental dysplasia of hip, diarrhea, vomiting etc. We excluded patients with genetic and metabolic disease, heart failure, intracranial bleeding, or infection. Totally, 115 infants were included into the study.

CDUS examinations were performed with 3.5 MHz convex transducers in longitudinal and transverse planes (iU22 Philips Healthcare, Best, the Netherlands; and Aplio, Toshiba Medical Systems, Japan).

BA was evaluated from anterior fontanelle by creating sagittal and coronal images. CDUS and spectral Doppler examinations were performed by placing the cursor in the middle portion of BA. PSV, EDV, and RI values were recorded (**Figure 1**). Patients were divided into 4 subgroups to analyze the change of normal values by age: (1) 0-120 days, (2) 121-180 days, (3) 181-270 days, (4) > 271 days.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) 25 for Windows (IBM SPSS Inc., Chicago, IL). Normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical were shown as median, minimum-maximum values. Categorical variables were shown as number and percentage. Consecutive variables were evaluated with Mann-Whitney U and Kruskal-Wallis tests. Spearman correlation analysis was used to define possible correlations between BA spectral Doppler parameters and age, sex.

RESULTS

Median age of the population was 69±2 days (1-367 days). 69 participants (60%) were males, 46 participants (40%) were females.

Normal values of PSV, EDV, and RI values according to age subgroups can be seen in **Table 1** and **Figure 2**. Median PSV, EDV, and RI values were found to be significantly different amongst age subgroups (**Table 1**, Kruskal-Wallis p value=0.001). According to Spearman correlation analysis results, a weak positive correlation was found between PSV, EDV values and age; meanwhile a weak but significant negative correlation was present between age and RI values (**Table 2**). We cannot find any correlation between sex and CDUS parameters.

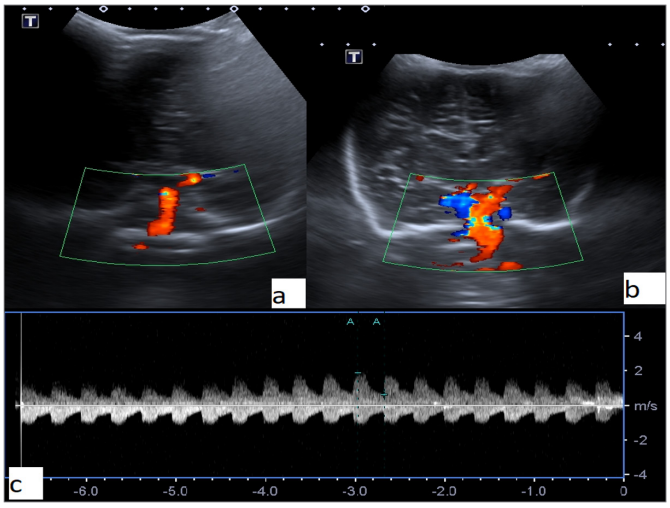

Figure 1. 153 days old healthy infant. CDUS images and spectral waveform acquired from basilar artery. PSV was 187.2 cm/s, EDV was 61.1 cm/s, RI was measured as 0.67.

Table 1. Median Basilar artery PSV, EDV, and RI values according to age

Age (days)	Number	PSV (cm/s)	EDV (cm/s)	RI	P values (KW/MWU)
0-120	75	113.4 (95.7-397.2)	30.2 (11.7-122.3)	0.71 (0.7-0.89)	P=0.001, P=0.03
121-180	22	153.3 (13.1-204.3)	53.2 (3.4-82.4)	0.62 (0.6-0.79)	P=0.001, P=0.04
181-270	14	164.8 (13.5-248.4)	75.8 (7.8-119.7)	0.54 (0.51-0.72)	P=0.001, P=0.001
271 and above	4	206.6 (186.8-247.2)	86,7 (77.9-101.1)	0.58 (0.54-0.59)	P=0.001, P=0.02
Whole population	115	131.9 (95.7-397.2)	44.8 (11.7-122.3)	0.66 (0.7-0.89)	

KW: Kruskal-Wallis, MWU: Mann- Whitney U, Note: Very low PSV, EDV and RI values were ignored in the table because these values are probably due to the crying effect.

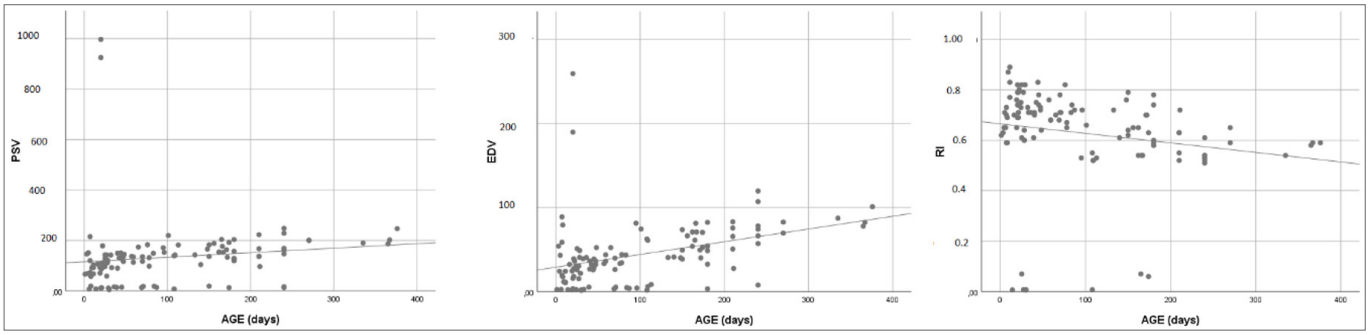

Figure 2. Scatterplots of median PSV, EDV, and RI values in healthy infant.

Table 2. Correlations between age and PSV, EDV, RI values

Correlations	PSV	EDV	RI
Age	r= 0.45 p= 0.00	r= 0.49 p= 0.00	r= (-) 0.42 p= 0.00
Sex	r= 0.11 p= 0.07	r= 0.21 p= 0.1	r= 0.22 p= 0.09

DISCUSSION

In the current study, we defined the normal PSV, EDV, and RI values of basilar artery in newborn, neonate, and infants. We found that normal values of mentioned parameters change by age, and there was no statistically significant difference between genders (p>0,05).

Blood flow of a vessel is affected from the difference of pressure between two ends of the vessel and the resistance of the vessel wall. Every major vessel has a characteristic CDUS pattern which is mainly created by PSV, EDV and RI values (11,12).

CDUS is an important tool for the evaluation of major vessels in pediatric patients with lacking ionizing radiation, being easy to access and cheap etc. (13). Although the CDUS characteristics of major cranial arteries have been defined in the literature, there is not sufficient information about the basilar artery to the best of our knowledge (5,6).

In the adult based study of Scheel et al. (14) if many studies compared, giving the name of the study will make it easy to understand), normal PSV value of BA was found as 131±21 cm/s. As far as we know, there was only one pediatric population-based study belongs to Binokay et al. (15) in the literature and according to the study's results, mean of PSV value was 84.7 cm/s. In our study, our median PSV value in the whole population was 131.1 cm/s. Our results were closer to the adult study than the pediatric study. The difference between the other pediatric population-based study and ours might be the result of populations' age characteristics; our median age was 69 days, mean age of the mentioned study was 10.2 years.

For vertebral artery, in neonates, PSV changes between 27–57 cm/sec and PSV value of internal carotid artery is defined between 47-73 cm/s (16,17). According to our data, median PSV value for the first 3 months of life was 131.1 cm/s, higher than vertebral and internal carotid arteries. The result is consistent with previous adult-based studies. Likewise, in adult-based studies, PSV values of BA are higher than PSV values of vertebral and internal carotid arteries (18,19).

In the adult-based study of Scheel et al. (14) normal EDV value of BA was defined as 39.9±8.1 cm/s . Whereas, in the pediatric population-based study of Binokay et al., mean EDV value was 49.5 cm/s (15). Our median normal EDV value was 39.1 cm/s, similar with adult values, slightly lower than the pediatric based study. The difference might be the result of populations' age characteristics, same as PSV values.

Two different studies belonging Kehrer et al. (16,17) including neonatal population, EDV values of vertebral and internal carotid arteries were respectively altered at the range of 5-11 cm/s and 13–21 cm/s. According to our results, EDV values of BA were higher than vertebral and internal carotid arteries. The results of another adult-based study of Schneel et al; EDV values of BA is also higher than EDV values of vertebral and carotid arteries like our study (19).

RI values can be calculated from PSV and EDV values via the formula (PSV-EDV)/PSV (20). In the literature, for adults, normal mean RI value of BA was defined as 0.58±0.10 (16,17). For infants, mean RI value was 0.41±0.17 (14).

According to the literature, the normal RI values of the internal carotid and vertebral arteries were ranged from 0.64 to 0.80 and from 0.73 to 0.89, respectively, in the neonatal population (17,18). Also, in full term neonates RI values of anterior, middle, and posterior cerebral arteries vary between 0.60 and 0.80 (9). These values were like our results (RI values of BA). We think that these similarities that do not change according to age population and the study also prove the reliability of our results.

According to a pediatric based study performed by Kehrer et al. (16) in healthy infants, EDV values of vertebral and internal carotid arteries increases with age. On the other hand, they cannot find any correlation between PSV values and age. In the same study, no significant correlation was defined between sex and CDUS parameters of vertebral/internal carotid arteries. As far as we know, there is no information about the correlation between CDUS parameters of BA and age/sex in the literature. Our results were partially consistent with the studies that discussed above. We cannot find any statistically correlation between sex and CDUS parameters (p>0,05). However, different from the literature, we defined a negative correlation between age and EDV, and a positive correlation between age and PSV. This subject is open for further prospective studies.

Considering the studies in the literature, flow velocities in all intracranial arteries decreased continuously from early childhood to adulthood and waveform parameters remained constant (21). This is probably due to the decrease in cerebrovascular resistance with age (22). In our study, arterial flow characteristics were found to be more like adults than children.

This study has some limitations including the small population number. We did not have any participants older than 1 years of age. Our results include only a small part of the pediatric population. Interobserver variability of CDUS parameters was ignored since only a small number of infants was evaluated by both authors. We have studied only with healthy infant, further studies including the cases with BA pathologies might help to define cut off values for abnormal cases. The technical limitations of the CDUS examination of the pediatric population, such as patient agitation and difficulty creating optimal waveforms, were also valid for our study.

PSV and EDV rates were extremely low in several patients. To the best of our knowledge, it is not known the exact reason but crying could have been a factor, altering brain hemodynamics and misleading RDUS measurements. In healthy humans, the Valsalva maneuver causes characteristic changes in flow velocity in the cerebral arteries, reflecting sympathetic and cerebral autoregulation responses, respectively. Considering crying and Valsalva maneuver is similar mechanism, this hypothesis can explain changes in the parameters of cranial Doppler ultrasonography. All of the children in our study were younger than 1 year old and cried from time to time during the examination. This effect is another limitation of our study (23).

As we tried to summarize and emphasize, there is not sufficient information about CDUS characteristics of BA. There is only one pediatric population based study in the literature (8), and it has different results with regard to our study; possibly as a result of examining different age groups. We believe that it is obviously needed to conduct further prospective studies including wide range of age groups, to define normal CDUS parameter ranges more precisely and correctly.

CONCLUSION

BA PSV, EDV and RI values change by age. No correlation is present between CDUS characteristics and sex. BA pathologies are rare in pediatric population, nevertheless knowing normal CDUS characteristics can help radiologists for an appropriate assessment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Keçiören Training and Research Hospital Ethics Committee (Approval date and number: 20.06.2018/ 2012-KAEK -11/2238).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Metastatic infectious complications in tunneled dialysis catheter-associated infections: a single-center experience

Ercan Türkmen

Ondokuz Mayıs University, Faculty of Medicine, Department of Nephrology, Samsun, Turkey

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ABSTRACT

Aim: Although the guidelines recommend arteriovenous fistula (AVF) primarily as vascular access in hemodialysis patients, tunneled catheter (TC) use is gradually increasing. TCs are associated with an increased risk of infection. TC infections can cause many metastatic infectious complications such as infective endocarditis (IE), spondylodiscitis (SpD), and paravertebral abscess. This study aimed to determine the frequency, risk factors, and prognosis of metastatic infectious complications in patients admitted to our hospital with TC infections.

Material and Method: Patients with TCs hospitalized to the Nephrology unit of Ondokuz Mayıs University Hospital between January 1, 2015, and January 1, 2020, with catheter infection, were included in the study. Demographic, clinical, and microbiological information was obtained from the patients' medical records retrospectively. Metastatic infectious complications were defined as IE, SpD, paravertebral or epidural abscess, and septic embolisms in any focus. Binary logistic regression analyzes were used to identify risk factors for metastatic infectious complications.

Results: One hundred and forty-eight catheter episodes were included in the study. Eighty-seven (58.8%) of the patients were women. Metastatic infectious complications developed in 22 (14.9%) of the patients. Of these, ten patients had IE, ten patients had SpD, and two patients had both IE and SpD. Coagulase-negative staphylococci was obtained as pathogenic microorganism in most cases (9/22, 49%). Patients with infectious complications had higher length of hospital stay [46.5 (10-171) vs 18 (6-92); p<0.001], and higher rates of sepsis (50% vs 16.7%; p<0.001), need for intensive care unit (36.4% vs 12.7%; p=0.005), and death (36.4% vs 11.9%; p=0.003). In multivariate binary logistic regression analysis, diabetes mellitus (DM) [OR: 7,813; 95% CI (2.05–29,783); p=0.003] and catheter duration [OR: 1.002; 95% CI (1-1,003); p=0.009] were identified as risk factors associated with metastatic infectious complications.

Conclusion: Metastatic infectious complications are associated with significant morbidity and mortality in hemodialysis patients. Long catheter duration and the presence of DM are risk factors for infectious complications. As recommended in international guidelines, minimizing the use of catheters and preventing the development of catheter infection by paying attention to basic hygiene rules, especially in diabetic patients, will help prevent these serious complications.

Keywords: Hemodialysis, infective endocarditis, metastatic complications, spondylodiscitis, tunneled catheter

INTRODUCTION

Among the renal replacement therapy options for end-stage renal disease patients, hemodialysis is the most preferred modality both in our country and all over the world (1). Arteriovenous fistula (AVF), synthetic AV grafts, or central venous catheters can be used as vascular access in hemodialysis patients. Although the guidelines recommend AVF primarily as vascular access in hemodialysis patients, central venous tunneled catheter (TC) use gradually increases (2).

Unfortunately, TCs are associated with significant morbidity and mortality in hemodialysis patients. In a meta-analysis, compared with persons with fistulas, those individuals using catheters had higher risks for all-cause mortality (risk ratio=1.53), fatal infections (2.12), and cardiovascular events (1.38) (3). Hospitalization rates for patients with TCs are more than twofold higher than those in patients with AVF (4). Infections are the most common cause of death in dialysis patients after cardiovascular causes (5). Local infections such as tunnel and exit site infections may occur in TCs, and bacteremia can also be seen. A Canadian study showed that during the first six months of dialysis, there is a high rate of bloodstream infection (BSI). In comparison to the AV

Corresponding Author: Ercan Türkmen, ercan.turkmen1907@gmail.com
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fistula, survival analysis revealed a relative risk of BSI of 8.49 (95% CI, 3.03–23.78) for TCs (6). Bacteremia can cause many metastatic infectious complications such as infective endocarditis (IE), spondylodiscitis (SpD), paravertebral abscess. These metastatic complications have also been shown to increase mortality and morbidity (7).

Our knowledge of metastatic complications in tunneled catheter infections is not sufficient. This study aimed to determine the frequency, risk factors, and prognosis of metastatic infectious complications in patients admitted to our hospital with tunneled dialysis catheter infections.

MATERIAL AND METHOD

The study was carried out with the permission of Ondokuz Mayıs University Clinical Researchs Ethics Committee (Date: 26.08.2021, Decision No: 2021/403). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was planned retrospectively. Patients with TCs hospitalized to the Nephrology unit of Ondokuz Mayıs University Hospital between January 1, 2015, and January 1, 2020, with catheter infection were included in the study. Patients with a temporary catheter and individuals under the age of 18 were excluded from the study.

Catheter-associated infection was defined as positive blood cultures or catheter cultures and no source of infection other than the catheter.

Demographic, clinical, and microbiological information was obtained from the patients' medical records. Data included age, gender, etiology of chronic kidney disease, duration of dialysis, clinical symptoms, and inflammation parameters [C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), white blood cell count] and biochemical parameters. Microbiological data included the type of microorganism and antimicrobial treatments. In addition, the treatments applied for the infected catheter (withdraw or exchange of catheter, transition to AVF, AV graft, or peritoneal dialysis) were also determined.

Metastatic infectious complications were defined as IE, SpD, paravertebral or epidural abscess, and septic embolisms in any focus. When vegetation was detected by echocardiography, the presence of IE was clinically confirmed and used in the analyses. The diagnoses of SpD, paravertebral and epidural abscess, and septic embolism were accepted as definitive diagnose when supported by clinical findings and characteristic changes detected in radiological evaluation.

When there was more than one episode of catheter infection in the same patient, each episode was considered as a separate patient in the analyses. However, since the primary endpoint was the presence of metastatic complication if a patient with metastatic infection continued with a catheter and re-infection developed, these episodes were not included in the analysis.

Statistical Analysis

All analyzes were conducted using the Statistical Package for the Social Sciences for Windows, version 25 (SPSS Inc., Chicago, IL, USA). Normality distribution was evaluated with the Shapiro-Wilk and Kolmogorov-Smirnov tests. The continuous variables were expressed as mean±standard deviation in the variables showing normal distribution and median (minimum-maximum) in those that did not show normal distribution. Categorical variables are expressed as percentages. Independent Samples T-test was used to compare non-dependent non-parametric variables in those with normal distribution, and Mann Whitney U test was used in those without normal distribution. The comparison of parametric variables was made with the Pearson Chi-Square test. Binary logistic regression analyzes were used to identify risk factors for metastatic infectious complications. P values <0,05 were considered statistically significant.

RESULTS

One hundred and forty-eight catheter episodes were included in the study. The median and mean ages of the patients were 62.5 (20-80) and 58.26±15.61 years, respectively. Eighty-seven (58.8%) of the patients were women. Diabetic nephropathy was the most common etiological cause of chronic kidney disease in 57 (38.5%) of the patients, while urological causes were the second most frequent. While 105 (70.9%) patients had hypertension, 21 (14.2%) patients had malignancy. The majority of patients (67.6%) had a right jugular catheter. The left jugular catheter was present in 41 (27.7%) patients, whereas the femoral catheter was present in only 7 (4.8%) patients. Fever was the most common complaint (85.1%) at admission. Eight (5.4%) of the patients had low back pain or neurological symptoms. Among the microbiological agents, the most common causative agent was staphylococci (53.4%), gram-negative bacilli were the second most common (25%). The culture was negative in 12.8% of catheter infection episodes.

Metastatic infectious complications developed in 22 (14.9%) of the patients. Of these, ten patients had IE, ten patients had SpD, and two patients had both IE and SpD. Paravertebral abscess accompanied in 7 (63.6%) of the patients with SpD. Mitral valve vegetation was detected in most patients with IE (7/11; 63.6%). While the

causative agent was coagulase-negative staphylococcus (9/22, 49%) in most of the patients with infectious complications, *S. aureus* was the causative agent in 6 (27.3%) patients. While 73 (49.3%) of the catheter infections were treated without catheter withdrawal or exchange, the catheter was exchanged in 59 (39.9%) episodes. Transition to AV fistula or peritoneal dialysis was performed in 16 (10.8%) episodes. Sepsis was observed in 32 (21.6%) episodes, and the need for intensive care developed in 24 (16.2%). In addition, the mortality rate was 15.5% (23/148).

Compared to those without metastatic infection, patients with infectious complications had higher ESR and CRP values, a higher incidence of diabetes mellitus (DM), longer catheter duration and length of hospital stay, and higher rates of sepsis, need for intensive care unit, and death. However, albumin levels were significantly low (**Table 1**). In multivariate binary logistic regression analysis, DM [OR: 7.813; 95% CI (2.05 – 29.783); p=0.003] and catheter duration [OR: 1.002; 95% CI (1-1.003); p=0.009] were identified as risk factors associated with metastatic infectious complications (**Table 2**). While 9 (40.9%) patients with metastatic infection were treated without catheter withdrawal or exchange, catheter exchange was performed in 6 patients (27.3%) with IE, 4 patients (18.2%) with SpD and one patient (4.5%) with IE and SpD. One patient was transitioned to AVF, and one patient to peritoneal dialysis.

Table 1. Comparison of demographic, clinical and laboratory characteristics of patients according to metastatic infectious complication status

	Metastatic infectious complication		t	p
	No (n=126)	Yes (n=22)		
Age, year	61 (20-80)	63.5 (28-80)	1182.5	0.272[b]
ESR, mm/h	79.88±32.39	96.33±31.63	-2.148	0.034[a]
CRP, mg/L	68 (0.3-482)	153.5 (17-306)	872	0.006[b]
Procalcitonin, ng/mL	8.58 (0.2-234)	6.65 (0.31-100)	1227	0.944[b]
ALT, U/L	9 (2-128)	9 (2-344)	1378.5	0.968[b]
AST, U/L	15 (4-171)	13 (5-328)	1354.5	0.865[b]
Albumin, gr/dL	3.34±0.73	2.91±0.57	2.634	0.009[a]
WBC, µL	9660 (197.1-31700)	10550 (1050-39460)	1169	0.242[b]
Hemoglobin, gr/dL	9.82±1.79	9.41±1.55	1.020	0.309[a]
Platelet, $\times 10^3$/ µL	182 (16.1-602)	167.5 (37-540)	1185	0.279[b]
Length of hospital stay, day	18 (6-92)	46.5 (10-171)	572	<0.001[b]
Catheter duration, day	202 (5-1880)	387.5 (18-2706)	975.5	0.027[b]
Dialysis vintage, month	15 (1-320)	13.5 (1-146)	1385	0.996[b]
Gender (Female), n (%)	76 (60.3)	11 (50)	0.823	0.364
Diabetes mellitus, n (%)	43 (34.1)	14 (63.6)	6.887	0.009
Hypertension, n (%)	86 (68.3)	19 (86.4)	2.98	0.084
Cardiovascular disease, n (%)	50 (39.7)	11 (50)	0.823	0.364
Malignancy, n (%)	17 (13.5)	4 (18.2)	0.338	0.561
Microbiological agent, n (%)			5.503	0.358
S. aureus	24 (19)	6 (27.3)		
CNS	41 (32.5)	9 (40.9)		
Gram-negative bacilli	33 (26.2)	4 (18.2		
Sepsis, n (%)	21 (16.7)	11 (50)	12.28	<0.001
ICU need, n (%)	16 (12.7)	8 (36.4)	7.72	0.005
Death, n (%)	15 (11.9)	8 (36.4)	8.537	0.003

a: Independent Samples T test, b: Man Whitney U test, ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; WBC: White blood count; CNS: Coagulase-negative staphylococcus; ICU: Intensive care unit.

Tablo 2. Univariate and multivariate binary logistic regression analysis of risk factors for metastatic infectious complication

Variables	Univariate		Multivariate	
	OR (%95 CI)	p	OR (%95 CI)	p
Age	1.023 (0.99-1.057)	0.180	1.001 (0.954-1.051)	0.955
Gender (Male)	1.52 (0.613-3.771)	0.366	2.378 (0.743-7.614)	0.145
Diabetes mellitus (Yes)	3.378 (1.315-8.678)	0.011	7.813 (2.05-29.783)	0.003
Hypertension (Yes)	2.946 (0.824-10.533)	0.097	1.783 (0.37-8.586)	0.471
Cardiovascular disease (Yes)	1.520 (0.613-3.771)	0.366	1.132 (0.343-3.734)	0.838
Malignancy (Yes)	1.425 (0.43-4.721)	0.562	3.185 (0.716-14.164)	0.128
Catheter localization				
Right jugular	Reference		Reference	
Left jugular/Femoral	0.967 (0.366-2.556)	0.947	0.852 (0.237-3.07)	0.807
Hemoglobin	0.869 (0.663-1.138)	0.307	0.873 (0.643-1.185)	0.384
S. aureus infection (Yes)	1.875 (0.657-5.351)	0.240	3.125 (0.917-10.643)	0.068
Catheter duration	1.001 (1.000-1.002)	0.014	1.002 (1-1.003)	0.009

OR: Odds ratio; CI: Confidence interval

DISCUSSION

Our study found the incidence of metastatic infectious complications in tunneled dialysis catheter infections to be 14.9%. We found long catheter time and the presence of DM to be risk factors for the development of metastatic infectious complications. We also showed that the length of hospital stay, sepsis, and mortality rates are higher in cases with complications.

International guidelines recommend AVF for long-term vascular access in hemodialysis patients. However, tunneled catheters are frequently used for reasons such as patient selection, initiation of dialysis under emergency conditions, and inability to open AVF to the patient. In a recent observational cohort study, the risk of developing catheter-related complications at one year was 30%, and the risk of bacteremia was 9%. In the second year, bacteremia increased to 11%. In the same study, bacteremia was found to be the most common cause of hospitalizations (73%) (8). A large meta-analysis showed that catheter use causes a 2-4 fold increase in the risk of fatal and non-fatal infections, with increased mortality (53%) and hospitalization (68%) compared to AVF (3).

Chronic kidney disease, hemodialysis, and especially a catheter as vascular access pose a risk for infectious complications such as IE and SpD (9-12). However, data on the frequency of infectious complications after bacteremia in hemodialysis patients are scarce. Mokrzycki et al. (13) found an infectious complication rate of 7% in their study. In our study, this rate was found to be 14.9%. However, since there is no other data in the literature, the necessity of new studies on its actual frequency is obvious.

On the other hand, although it is known that catheter use in hemodialysis patients increases the risk of infection, our information on the factors affecting complications is not sufficient. Mokrzycki et al. (13) reported that the only variable in a multivariate analysis that was significantly associated with the development of an infectious complication was infection with *S. aureus*. Similarly, the most common causative organism in developing IE or SpD in dialysis patients is *S. aureus* (10,14,15). Parallel to these, complications are common in *S. aureus* bacteremia developing in hemodialysis patients, and it has been shown that 17% of the patients develop IE, and 5.7% of them develop osteomyelitis (16). In our study, *S. aureus* was found to be the causative agent in 6 of the patients who developed complications, but it was not detected as a risk factor for the development of complications in the multivariate analysis. Most of our patients were found to be coagulase-negative staphylococcal factors. In other studies in the literature, similar to ours, it is noteworthy that staphylococci are the most common factor in cases that develop both IE and SpD.

In our study, the presence of DM and the catheter duration were determined as risk factors for complications. Diabetes creates susceptibility to infections by affecting both cellular and humoral immunity (17). In a study conducted on a large group of hemodialysis patients with catheters, DM increased the risk of developing catheter infection 2.37 times (18). On the contrary, some studies show that DM does not cause an increase in the risk of infection (8,19). However, there is no previous study showing that DM poses a risk for metastatic infectious complications. In our study, DM was found to be a severe risk factor for the development of metastatic infectious complications (OR:7.8). It is known that there is a relationship between the duration of the catheter and the development of catheter-related infections. Lemaire et al. (18) found that a catheter duration of >90 days increased the risk of infection. Shingarev et al. (20) determined that there was a serious increase in the rate of infected patients with the increase in the duration of the catheter (35% at the 3rd month vs. 79% at the 12th month).

Studies show that the catheter location (left internal jugular vein or femoral veins) is associated with an increased risk of infection (21,22). However, on the contrary, it has been shown in many studies that catheter location is not one of the risk factors associated with the development of infection (23,24). It has even been found that infection rates in femoral tunneled catheters are similar to those in jugular catheters (19,25). It is not known whether the catheter location poses a risk for metastatic infectious complications. However, in our study, we did not find a relationship between the catheter location and the development of complications.

Our study found both the length of hospital stay and mortality rate significantly higher in patients with complications than those without complications. In addition, the development of sepsis and the need for intensive care were higher in these patients. The median length of stay was 46.5 days, and the mortality was 36.4% in patients with complications. Considering that patients should receive intravenous treatment for an average of 6 weeks, the length of hospital stay was prolonged. Similar or even longer lengths of hospital stay are observed in other studies in the literature (14,15). The length of stay in hospital also differs significantly higher when compared with the non-dialysis population (26). Severe infections in patients with complications have led to sepsis, in parallel, to an increase in the need for intensive care. In addition, disease severity is also associated with increased mortality rates. Although the mortality rate was relatively high in our study, similarly, the mortality rate in other studies in the literature ranged between 20% and 46% (14,15,26-28).

Our study has some limitations. First of all, the most important limitations are that it is retrospective, and it was performed only in patients hospitalized in a single-center or even only in the nephrology unit. In addition, the fact that our patients were only patients with TCs may not reflect the incidence of infectious metastatic complications in all hemodialysis patients. However, since TCs are be preferred in the long-term treatment of patients, we think that it is more accurate to determine the frequency in patients with TCs.

CONCLUSION

Our study showed that metastatic infectious complications (infective endocarditis and spondylodiscitis) are common in TCs related infections. The length of hospital stay and mortality rates increase in patients with metastatic infectious complications. Long catheter duration and presence of DM were identified as risk factors for metastatic infectious complications. As recommended in international guidelines, minimizing the use of catheters and preventing catheter infection by paying attention to basic hygiene rules, especially in diabetic patients, will help prevent these serious complications

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 26.08.2021, Decision No: 2021/403).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: Part or all of the manuscript is not published elsewhere and is not in the process of being evaluated in another journal at the same time. But it was presented as an oral presentation at '23. Ulusal Hipertansiyon and Böbrek hastalıkları Kongresi- 17-22 Eylül 2021, Girne-Kıbrıs'

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The effect of diabetes on mid-term survival of open heart surgery patients aged over 70 years

İlker İnce[1], Levent Altınay[2]

[1]Health Sciences University, Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Cardiovascular Surgery, Ankara, Turkey
[2]Zonguldak Bülent Ecevit University, Faculty of Medicine, Department of Cardiovascular Surgery, Zonguldak, Turkey

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ABSTRACT

Aim: To determine the effect of diabetes on mid-term survival rates of the patients over 70 years of age who underwent an open heart surgery.

Material and Method: Patients who underwent an open heart surgery between November 2016 and May 2019 in our center included in this retrospective study. The patients younger than 70 years were excluded. Patients were divided into two groups: Group 1 included diabetic patients, Group 2 included non-diabetic patients. The patients who were followed-up for less than 24 months were excluded.

Results: A total 389 patients were evaluated and 93 (23.9%) patients aged over 70 years were included in this retrospective study. Group 1 included 36 (38.7%) type 2 diabetic patients and Group 2 included 57 (61.3%) non-diabetic patients. The general mean follow-up time was 48.25±10.42 months (range between 30.83-77.07 months). The number of emergency operations was significantly higher in non-diabetic patients group (p= 0.005). The mortality rates were similar in both groups (30.55% in Group1, 35.08% Group 2, p= 0.652). The survival times of the groups were also similar (63.49±3.42 months in diabetic patients, 59.40±2.67 months in non-diabetic patients group, p= 0.254).

Conclusion: Diabetes mellitus has no effect on the mid-term survival rates of the older patients who underwent open heart surgery.

Keywords: Cardiac surgical procedures, diabetes mellitus, survival rates, coronary artery bypass, heart valve diseases

INTRODUCTION

The physiological and anatomical changes occur in both the heart and the vessels as the age of patient increases. These patients may present normal hemodynamic performance at rest, but their cardiac capacity can reach to the limits very quickly in stress situations such as open heart surgery (1). Increased life expectancy, changes associated with end-of-life morbidity, duration of diabetes and other comorbidities in older patients increase the difficulty of the management of health care of these patients (2,3).

Diabetes is one of the major risk factors for major adverse cardiovascular events in the cardiac disease patients (4,5). Also, cardiovascular diseases are reported as the leading cause of mortality in diabetic patients (6). The duration of diabetes is related to the higher incidence of complications and uncontrolled glycemia (7,8).

Herein, we aimed to determine the effect of diabetes on the mid-term survival rates of the patients over 70 years of age who underwent an open heart surgery.

MATERIAL AND METHOD

The study was carried out with the permission of Zonguldak Bülent Ecevit University Clinical Researchs Ethics Committee (Date: 18.09.2019, Decision No: 2019-146-18/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who underwent an open heart surgery between November 2016 and May 2019 in our center were evaluated. The patients younger than 70 years were excluded. The previous diagnosis of type 2 diabetes mellitus and using an anti-diabetic therapy at the time of surgery were the inclusion criteria. The patients who had type 1 diabetes mellitus were excluded. The patients with high blood glucose levels but didn't have previous diagnosis of diabetes and were not using an anti-diabetic regime, were accepted as stress-induced hyperglycemia and were excluded. The patients who were followed-up for less than 24 months were excluded.

Corresponding Author: Levent Altınay, laltinay@gmail.com
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The study patients were divided into two groups. Group 1 included the patients with type 2 diabetes mellitus and Group 2 included non-diabetic patients. The patient data were collected retrospectively from the institutional database. Any oral antidiabetic drugs were ceased 24 h before surgery and insulin therapy was conducted according to the internal medicine specialist consultation in elective surgery patients. Lactic acidosis was defined as arterial lactate concentration exceeding 5 mmol/L and pH ≤ 7.35 (9). Peak lactic acid levels measured in blood gas analysis in the intensive care unit (ICU) period were taken to compare the lactic acidosis levels between the patient groups.

Statistical analysis: The SPSS (Statistical Package for the Social Sciences) v16 software was used for statistical analysis of the data. Continuous data were expressed as means±standard deviation and categorical data were expressed as percentages. The normality of the distribution of the data was tested with Kolmogorov-Smirnov test. The non-parametric data of the groups were tested with chi-square and Fisher's exact tests. The parametric data of the groups were tested with Student's t-test. P value <0.05 was accepted as statistically significant.

RESULTS

A total 389 patients were evaluated and 93 patients aged over 70 years were included in this retrospective study. Group 1 included 36 (38.7%) type 2 diabetic patients and Group 2 included 57 (61.3%) non-diabetic patients. The incidence of peripheral artery disease (PAD) was significantly higher in Group 1 (26 (72.22%) patients in Group 1 vs 20 (35.08%) patients in Group 2, p<0.001). The incidence of cerebrovascular events was significantly higher in Group1 (13 (36.11%) patients in Group 1 vs 8 (14.03%) patients in Group 2, p=0.013). The mean time of duration of diabetes in Group 1 was 23.94±13.02 years (ranged from 5 to 49 years). There were no statistically significant differences between the other preoperative variables of the groups. The preoperative data of the groups is presented in **Table 1.** The most commonly used antidiabetic agent in the study cohort was metformin. The medication types of diabetic patients are presented in **Table 2**.

The general mean follow-up time was 48.25±10.42 months (range between 30.83-77.07 months). The number of emergency operations was significantly higher in non-diabetic patients group (p= 0.005). The mortality rates were similar in both groups (30.55% in diabetic patients, 35.08% in non-diabetic patients group, p= 0.652). The survival times of the groups were also similar (63.49±3.42 months in diabetic patients, 59.40±2.67 months in non-diabetic patients group, p= 0.254) (**Figure 1**). There were no significant differences in other postoperative data (**Table 3**).

Table 2. Antidiabetic medication

	Number	Percent (%)
Metformin	17	47.22
Metformin+Insulin	5	13.99
Insulin	10	27.78
Empagliflozin	4	11.11

Table 1. Preoperative data

	Diabetic patients (n=36)	Non-diabetic patients (n=57)	P value
Male n (%)	25 (69.44)	34 (59.65)	0.339
Hypertension n (%)	20 (55.56)	36 (63.16)	0.466
Hyperlipidemia n (%)	12 (33.33)	11 (19.30)	0.127
COPD n (%)	7 (19.44)	12 (21.05)	0.851
PAD n (%)	26 (72.22)	20 (35.08)	<0.001
CVE	13 (36.11)	8 (14.03)	0.013
Tobacco abuse n (%)	12 (33.33)	12 (21.05)	0.176
Thyroid dysfunction n (%)	7 (19.44)	9 (15.79)	0.649
Fasting glucose mg/dL mean±SD	192.81±55.57	112.65±28.17	<0.001
HbA1c mean±SD	7.88±1.80	5.51±0.63	<0.001
BMI mean±SD	27.31±3.52	27.43±3.87	0.915
Blood urea mean±SD	63.06±38.92	51.25±18.52	0.439
Blood creatinine mean±SD	1.20±0.64	1.08±0.52	0.249
Preoperative EF mean±SD	48.47±10.32	48.81±9.03	0.955
Preoperative diagnosis n (%)			0.100
CAD	30 (83.33)	40 (70.17)	
CAD+Valve disease	1 (2.77)	3 (5.26)	
CAD+Carotid disease	2 (5.55)	2 (3.50)	
Valve disease	2 (5.55)	1 (1.75)	
Aortic disease	1 (2.77)	11 (19.29)	

COPD: Chronic obstructive pulmonary disease; PAD: Peripheral artery disease; CVE: Cerebrovascular event; BMI: Body mass index; SD: Standard deviation; EF: Ejection fraction. CAD: Coronary artery disease.

Table 3. Postoperative data			
	Diabetic patients (n=36)	Non-diabetic patients (n=57)	P value
Emergency operation	2 (5.55)	17 (29.82)	0.005
IABP	12 (33.33)	10 (17.54)	0.081
ONBHCAB	2 (5.55)	2 (3.50)	0.640
OPCAB	2 (5.55)	5 (8.77)	0.559
Exitus	11 (30.55)	20 (35.08)	0.652
CPB min mean±SD	107.92±87.96	94.84±91.60	0.368
XCL min mean±SD	52.92±38.84	45.09±42.28	0.219
Peak lactic acid mmol/L mean±SD	4.15±0.76	3.96±1.00	0.299
ICU stay days mean±SD	4.73±12.78	6.04±12.59	0.346
In-hospital stay days mean±SD	9.53±10.77	12.25±16.73	0.523
Follow-up time months mean±SD	49.01±11.48	47.76±9.78	0.449
Survival time months mean±SD	63.49±3.42	59.40±2.67	0.254

IABP: Intra-aortic balloon pump; ONBHCAB: On-pump beating heart coronary artery bypass; OPCAB: Off-pump coronary artery bypass; CPB: Cardio-pulmonary bypass; SD: Standard deviation; XCL: Aortic cross-clamp; ICU: Intensive care unit.

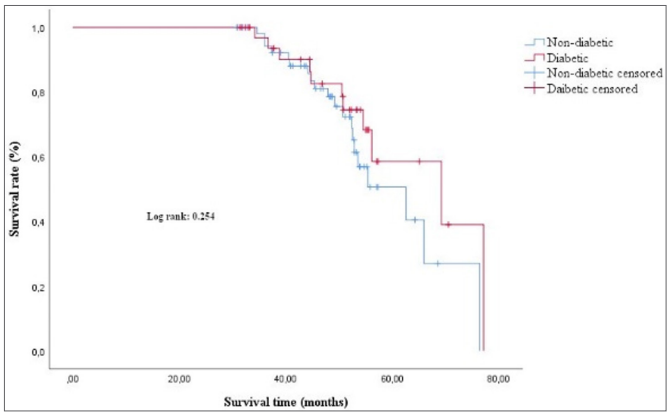

Figure 1. Survival curve related to postoperative survival of diabetic and non-diabetic patients.

DISCUSSION

The results of this study show that diabetes mellitus have no effect on the mid-term survival and mortality rates of the patients aged over 70 years who underwent open heart surgery.

Age is a generally accepted risk factor for morbidity and mortality after cardiac surgery in the risk scoring systems (10,11). The number and severity of comorbidities such as diabetes mellitus, left ventricular dysfunction, chronic obstructive pulmonary disease, etc. increase in this aged population and these comorbidities also affect the postoperative prognosis of these patients (10).

Wang et al. (12) reported 29% 5-year mortality rate in patients >80 years after cardiac surgery. Also they reported diabetes a significant risk factor for long term survival with a hazard ratio 1.98 regardless of age (p=0.011) (12). Afilalo et al. (13) reported a decline in the survival curve in one year to two years' period after cardiac surgery in the patients aged >75 years. Likosky et al. (14) reported a median survivorship 7.4 years of patients aged 80-84 years and 5.8 years of patients aged over 85 years. They also reported diabetes mellitus a significant risk factor for long term survivorship with a hazard ratio 1.51 (CI 95% 1.45, 1.57, p=0.001).

Schwann et al. (15) followed 11,931 patients who underwent isolated coronary artery bypass grafting (CABG) surgery for an average of 8.7±4.4 years including 4377 diabetic patients and reported significantly higher mortality rates in diabetic patients versus non-diabetic patients (37.1% vs 28.6% respectively, p<0.001).

In 3-years results of SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) study, it was reported that significantly lower postoperative major adverse cardiac events occurred in CABG patients when compared to the patients who underwent percutaneous coronary revascularization with drug-eluting stents in the presence of diabetes (16). In our study, the mid-term survival and mortality rates were not significantly different in diabetic patients when compared to non-diabetic patients.

The emergency operation and off-pump coronary bypass (OPCAB) surgery rates were significantly higher in non-diabetic patients in our study. We think that this was because of selection bias or incidental.

The duration of diabetes is related to the course of the disease especially in type 2 diabetes. Huang et al. (17) reported that, age and duration of diabetes are independent predictors of the clinical outcome of the disease in older (aged over 60 years) patients. They also reported that, the incidence of the complications such as end-stage renal disease, eye disease, stroke, heart failure, mortality increases as the age of the patient and the duration of the diabetes increase. But their study was not focused on the patients who underwent open heart surgery.

There are different types of antidiabetic drugs such as insulin, alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists), meglitinides, sodium-glucose transporter (SGLT) 2 inhibitors, etc. There are many studies reported

that SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin) reduce the adverse cardiovascular events in patients with type 2 diabetes (18–22). In the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) study which was published in 2015, it was reported that empagliflozin (one of the SGLT-2 inhibitors) reduced the rates of major adverse cardiovascular events by 14%, cardiovascular death by 38%, all-cause mortality by 32% in people with type 2 diabetes mellitus and coronary artery disease (18). Verma et al. (22) published subgroup analysis of this study in 2018 including the patients who had a previous history of coronary artery bypass graft (CABG) surgery and reported that adding empagliflozin to the standard antidiabetic medication reduced the risk of cardiovascular death by 48% and all-cause mortality by 43%. In a recent meta-analysis, it was reported that metformin, a commonly used oral antidiabetic drug in type 2 diabetes, reduced the rates of cardiovascular and all-cause mortalities and cardiovascular events in coronary artery disease (CAD) patients with type 2 diabetes (23). Its undeniable that metformin and empagliflozin have positive effects on preventing the cardiac adverse events in type 2 diabetic patients with CAD. The cohort of our study included the patients who underwent any kind of open heart surgery so we think that is a research subject that if metformin and empagliflozin have any effects on the postoperative cardiac events of these patients too.

Some rare adverse events such as metformin associated lactic acidosis (MALA) can be seen due to metformin therapy (24). The incidence of MALA was reported as 3.3-9.7 cases per 100 000 patient-years and the mortality rate was up to 45% (25,26). On the contrary, Nazer et al. (27) reported that metformin was not associated with lactic acidosis in diabetic patients undergoing CABG operation. In this study, the peak lactic acid levels were slightly higher in diabetic patient group but it was not statistically significant.

Being overweight and obesity are common problems of patients with Type 2 diabetes. These patients need higher doses of insulin therapy to maintain the normal levels of glycemia as the disease progresses.Varol et al. (28) reported that losing weight may reduce the need for insulin and other antidiabetic drugs. We think that body weight control may also reduce postoperative adverse events such as reactive hypoglycemia, impaired wound healing, sternal dehiscence, etc after cardiac surgery.

The limitations of the study are its retrospective design and it is a one-center study. Also we could not perform oral glucose tolerance test in all of the patients because of the lack of patient cooperation. The medical history had to be taken from the patient's relatives but not the patient herself/himself because of the diminished cognitive functions of the patients. We could not assess the effect of antidiabetic medication on the cardiac results of the patients because most of the patients used different types of drugs for various durations through the course of their disease.

CONCLUSION

Diabetes mellitus has no effect on the mid-term survival rates of the older patients who underwent open heart surgery. Also the mortality rates of these patients seem to be unaffected by the presence of diabetes but more studies should be conducted on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zonguldak Bülent Ecevit University Clinical Researchs Ethics Committee (Date: 18.09.2019, Decision No: 2019-146-18/09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Relationship between mental symptoms, dietary compliance and glucose levels of diabetic patients in isolation during COVID-19 Pandemic

Seda Erem Basmaz[1], Fatma Doğan[2], Fatime Şahin[3]

[1]Health Sciences University, Derince Training and Research Hospital,Department of Endocrinology and Metabolism Diseases, Kocaeli, Turkey
[2]Tuzla State Hospital, Department of Psychiatry, İstanbul, Turkey
[3]Karabük University, Karabük Training and Research Hospital, Karabük, Turkey

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ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19, 2019-nCoV) which first appeared in Wuhan, China in December 2019 is a disease causing acute respiratory failure. Home isolation methods are used to control the disease all around the world and also in our country. In this study we planned to explain the relationship between some mental symptoms, diet compliance, frequency of blood glucose measurement and blood glucose levels in diabetic patients during home isolation.

Material and Method: In this study some questions about the frequency of blood glucose measurement, blood glucose levels, dietary compliance and mental states of the patients were asked on the phone and the patients were asked to give a score to the symptom severity. The notes were retrospectively screened.

Results: It is known that social isolation triggers the anxiety and depression. Anxiety and depression can increase the secretion of some hormones which leads high blood glucose levels (respectively 54.4% of those with 200-300 mg/dl, 91.7% of those with >300 mg/dl don't follow their diets) in diabetic patients. These symptoms can reduce dietary compliance and frequency of the blood sugar measurement, therefore can make metabolic control of the diabetes difficult.

Conclusion: In this study, we found that blood glucose levels were very high and the frequency of blood glucose measurements were very low in the patients who had some mood changes and we saw that the patients did not follow on their diets. It is important to support patients mentally during this process. Training and following up should be used with some various methods.

Keywords: COVID 19, anxiety, home isolation, phone visits

INTRODUCTION

Coronavirus 2019 (COVID-19, 2019-nCoV) which first appeared in Wuhan, China in December 2019 is a disease causing acute respiratory failure (1). It has been defined as a serious health problem in the world. Diabetes and its comorbidities have high mortality risk (2). The severity of COVID-19 and its mortality course have been shown to be associated with cardiovascular diseases, diabetes, hypertension, chronic lung and kidney diseases, and cancers (3).

Elderly people and people with chronic disease such as diabetes and hypertension seem to be more vulnerable to coronavirus infection. It was reported that the overall proportion of diabetes in COVID-19 increased from 5.3% to 20% (4).

COVID-19 infection can rapidly proceed towards acute respiratory distress syndrome and septic shock, leading to multi-organ failure in diabetic patients. It is shown that diabetes is associated with the mortality increase (4).

As a general perception and epidemiological studies show that diabetes is thought to increase the mortality and morbidity during infectious diseases. It is not yet known if diabetes is a risk factor in the prognosis of COVID-19 infection. It is known that type 2 diabetes and obesity can cause chronic and low-level inflammation. Moreover viral infections can cause sharp fluctuations in glucose levels in diabetic patients (5).

Corresponding Author: Seda Erem Basmaz, s_erem@hotmail.com
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According to American Diabetes Federation, blood glucose monitoring is quite an important component for diabetes regulation (6). Glucose regulation in diabetic patients should be important during COVID-19 infection (4). Due to the increase in mortality and morbidity, especially in the elderly and people with chronic diseases, home quarantine has been applied to these people all over the world and in our country during COVID-19 infection.

During the pandemics social isolation and quarantine could trigger anxiety and depression. Similar situations have been observed in people who were kept away from the people they love, from their personal habits and life-styles. This can cause disappointment, boredom and depression. Avoiding infectious diseases can increase anxiety. This anxiety situation may increase even more with improper social avoidance guidelines, less reliable media sources (7).

In 2003 severe acute respiratory syndrome (SARS) was accepted as an epidemic and it affected 8000 people in 30 countries. During this period several mental symptoms appeared in SARS patients. These mental symptoms are generally anxiety and depression. Between 2005 and 2006 in Hong Kong 47.8 % of the 1394 patients with SARS were diagnosed with post-traumatic stress disorder and this situation continued for about 30 months in 25.6% of these patients (8).

A few studies have been conducted searching mental health situation of those surviving after natural disasters and infectious diseases. However, no study has been conducted to explain the relationship between the risk of infection and mental health in isolated individuals.

It is found out that 80 % of the population were afraid of MERS infection during the MERS epidemic. Those who were isolated for more than two weeks after contacting people with MERS infection showed serious anxiety symptoms and fear. Mortality rate of MERS is well known and it is approximately around 20 %. Patients who were diagnosed with the disease and kept in isolation for more than 2 weeks developed fear. But the effects of the two-week isolation on mental health are not known (8).

During the infection, stress and anxiety can increase the secretion of some hormones (cortisol, catecholamine etc.) of which would increase the blood glucose levels and its complications in diabetic patients (4).

In this study we planned to explain the relationship between some mental symptoms, dietary compliance, frequency of blood glucose measurement, and blood glucose levels in diabetic patients during home isolation.

MATERIAL AND METHOD

This study was performed with the approval of the ethics committee of Medical University of Vienna in accordance with the principles of the Helsinki Declaration of 1964 and its further amendments. The study was carried out with the permission of Karabük University Ethics Committee (Date 18.06.2020, Decision No 2020/279).

Phone visits were made to patients regularly in our diabetic outpatient clinic. During the COVID-19 pandemic, we increased phone interviews with diabetic patients (n: 298) who had to stay at home. We asked the patients some questions about their ages, type of their diabetes, age of diabetes, usage of insulin, if they used insulin we asked the frequency of injections in a day, how many times they would measure their blood glucose, how their measurement levels (average of the last 3 measurements) and dietary compliance were. We also asked if they had any mental symptoms such as depression, anxiety, tension or excitement and wanted them to give a score (from 0 to 6). We chose our questions from the Turkish Version of the Brief Psychiatric Rating Scale. The reason why we reduced the number of questions was not to extend the call time on the phone. According to the scaling 0 is determined as none, 1-2 as mild, 3-4 as medium, 5-6 as severe. According to the scores given by the patients, those who selected mild and medium were given simple behavioral advice. Those who selected severe were suggested to take psychiatric control besides behavioral advice. If the patient's glucose levels were high and if they didn't follow their diets properly, they were advised to follow their diet and to come for a check-up especially. In this study the notes taken during the phone interviews were retrospectively screened.

Statistical Analysis

The information about the patients was gathered and uploaded. Continuous variables (such as measurement values, scale score averages etc.) were stated as mean±standard deviation. Linear relationship between variables was tested by the Spearman correlation test. For the analyses between categorical variables, Chi-square Test was used. Analyses were realized by using IBB SPSS (Statistical Package Program for the Social Sciences) version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was taken as $p<0.05$.

RESULTS

The average age of the patients was 50.30±13.42 (59.7% of them between 41-60 years old), 64.7% percentage of the patients were women (n=194), 79.3% percentage of the patients were with type 2 diabetes (n=238), and 67.7% percentage of the patients use insulin (n=203). While the percentage of those who use insulin once a day was 31.6%, the percentage of those who use insulin four

times a day was 55.6%. 85.3% of the patients (n=255) expressed that they were measuring their glucose levels themselves during the coronavirus pandemic. It was found that while the percentage of those who say the frequency of measurement was once a day was 32.1 % (n=59), the percentage of those who say twice a day was 37.9% (n=69). The percentage of patients with 100-199 mg/dl blood glucose level was 63.2%, those with 200-300 mg/dl was 19.9% and those with >300 mg/dl was 4.1%. 57.3% of the patients (n=172) said they followed their diet during this period (**Table 1**).

Table 1. Comparison of the results evaluated after the visit by age in terms of some descriptive features

	n (%)
Age (year)	
18-40 age	61 (20.5%)
41-60 age	178 (59.7%)
>60 age	59 (19.8%)
Gender	
Female	194 (64.7%)
Male	106 (35.3%)
Type of diabetes	
Type 1 diabetes	62 (20.7%)
Type 2 diabetes	238 (79.3%)
Usage of Insulin	
Yes	203 (67.7%)
No	97 (32.3%)
Frequency of Insulin usage (daily)	
1	62 (31.6%)
2	18 (9.2%)
3	7 (3.6%)
4	109 (55.6%)
Measuring realised?	
Yes	255 (85.3%)
No	44 (14.7%)
Measurement frequency (daily)	
1	59 (32.1%)
2	69 (37.9%)
3	11 (6.4%)
4	28 (15.1%)
5 and more	14 (7.5%)
Measurement frequency (weekly)	
0	2 (2.5%)
1	49 (61.3%)
2	20 (25.0%)
3	8 (10.0%)
4	1 (1.3%)
Measurement values (mg/dl)	
does not know	38 (12.8%)
100-199	187 (63.2%)
200-300	59 (19.9%)
>300	12 (4.1%)
Dietary compliance	
Yes	172 (57.3%)
No	128 (42.7%)
Total	293 (100%)

When we evaluate all the followed diabetic patients according to their glucose level, we found out that 71.1% of those who don't know their glucose level. Patients with high level glucose level (respectively 54.4% of those with 200-300 mg/dl, 91.7% of those with >300 mg/dl don't follow their diets; on the contrary, 69.0 % of the patients (n=129) with regular glucose level (those with between 100-199 mg/dl) follow their diets (p<0.001).

It was statistically found out that the higher the blood glucose level was, the more significantly the rates of those with severe anxiety, tension and depression symptoms (excluding >300 mg/dl) increased (p=0.004). On the other hand no significant relation was found out between the excitement level and blood glucose level (**Table 2**).

Table 2. Comparison of compliance with diet, anxiety, tension, depression and excitement levels according to blood sugar levels.

	Blood Glucose Level					p
	does not know	100-199 mg/dl	200-300 mg/dl	>300 mg/dl	Total	
Dietary compliance (n,%)						<0.001*
no	27 (71.1%)	58 (31.0%)	32 (54.2%)	11 (91.7%)	128 (43.2%)	
yes	11 (28.9%)	129 (69.0%)	27 (45.8%)	1 (8.3%)	168 (56.8%)	
Score of anxiety symptoms (n,%)						0.004*
None	12 (31.6%)	43 (23.0%)	8 (13.6%)	1 (8.3%)	64 (21.6%)	
Mild	11 (28.9%)	54 (28.9%)	14 (23.7%)	5 (41.7%)	84 (28.4%)	
Medium severe	13 (34.2%)	60 (32.1%)	16 (27.1%)	1 (8.3%)	90 (30.4%)	
Severe	2 (5.3%)	30 (16.0%)	21 (35.6%)	5 (41.7%)	58 (19.6%)	
Score of tension symptoms (n,%)						0.006*
None	10 (26.3%)	55 (29.4%)	11 (18.6%)	1 (8.3%)	77 (26.0)	
Mild	19 (50.0%)	60 (32.1%)	13 (22.0%)	5 (41.7%)	97 (32.8)	
Medium severe	7 (18.4%)	50 (26.7%)	20 (33.9%)	2 (16.7%)	79 (26.7)	
Severe	2 (5.3%)	22 (11.8%)	15 (25.4%)	4 (33.3%)	43 (14.5)	
Score of depression symptoms (n,%)						0.012*
None	11 (28.9%)	49 (26.2%)	7 (11.9%)	1 (8.3%)	68 (23.0%)	
Mild	16 (42.1%)	66 (35.3%)	15 (25.4%)	7 (58.3%)	104 (35.1%)	
Medium severe	8 (21.1%)	46 (24.6%)	21 (35.6%)	4 (33.3%)	79 (26.7%)	
Severe	3 (7.9%)	26 (13.9%)	16 (27.1%)	0 (0.0%)	45 (15.2%)	
Score of excitement symptoms (n,%)						0.167*
None	8 (21.1%)	42 (22.5%)	4 (6.8%)	0 (0.0%)	64 (22.2%)	
Mild	11 (28.9%)	54 (28.9%)	15 (25.4%)	4 (33.3%)	81 (28.1%)	
Medium severe	10 (26.3%)	53 (28.3%)	21 (35.6%)	4 (33.3%)	85 (29.5%)	
Severe	9 (23.7%)	38 (20.3%)	19 (32.2%)	4 (33.3%)	58 (20.1%)	
Total	38 (100%)	187 (100%)	59 (100%)	12 (100%)	296 (100%)	

* Chi-square Test

DISCUSSION

For the last few months, COVID-19 pandemic has been the most important disease in the world. Because of having a high mortality rate and high infection rate, COVID-19 causes great fear in people (9). Higher rates of comorbidities, such as hypertension (HT) and diabetes mellitus (DM), are also observed in patients hospitalized for severe disease (10).

In the management of COVID-19, home isolation has used in our country and all around the world. It is known from previous pandemics that isolation and quarantine trigger depression and anxiety (7). In this study, 298 patients with diabetes who had to stay at home we contacted by phone and asked questions about their frequency of blood glucose measurement, glucose levels, dietary compliance and mental conditions.

Some studies showed diabetes is observed as 5.6% in men and 4.2 % in women. In the whole population the diabetes prevalence increases in both sexes (11). In our study, prevalence was found at similar rates (64.7% female, 35.3% male).

Type 1 and 2 diabetes take a great role in the etiological classification of diabetes. 85% of these are type 2 diabetes (12). In our study 79.3% percentage of the patients are with type 2 diabetes as well.

It was observed that a great majority of patients use insulin and apply multiple injections. 85.3% of the patients were checking their blood glucose. When more asked, it was found that measurement frequency was quite few. The rate of the patients who were measuring 5 or more times a day was 7.5%. Besides 12.8% of the patients didn't know the course of blood glucose. It was especially stated that blood glucose measurement is compulsory in diabetes management (13).

In another study, regardless of diabetes treatment, it is found that frequency of blood glucose measurement is related with the significant decrease in HgbA1c (14).

In our study we found out that the frequency of blood glucose measurement was not satisfactory. This situation may cause the deterioration of blood glucose regulation, dietary compliance and auto control. We think that patients should be encouraged more and given necessary training about the issue and we called them again.

Diet has an important role to control blood glucose regulation. Medical nutrition treatment possesses an important role in diabetes management and self-management.

In the United Kingdom (UK) Prospective Study (UKPDS) a total of 30.444 people with type 2 diabetes were taken. In the whole treatment and control groups it was shown that people who were on a diet as primary protection in the first three months at the beginning of the study lost approximately 5 kilos and there was 46 mg/ dl decrease in fasting plasma glucose and 1.9% in HgbA1c (15).

In our study, we found out that 71.1% of those who don't know their blood glucose level, and patients with high level blood glucose level (respectively 54.4% of those with 200-300 mg/dl, 91.7% of those with >300 mg/dl) don't follow their diets; on the contrary, 69.0 % of the patients (n=129) with regular blood glucose level (those with between 100-199 mg/dl) follow their diets. We showed the importance of medical nutrition therapy in the diabetes regulation in our study. During the calls we made recommendations on the issues we realized to the patients who don't follow their diets.

In the meta-analysis, anxiety seems to be quite common in diabetes. Generalized anxiety was found in 15% of the patients and anxiety symptoms were increased in 40% of the patients. In the same meta-analysis, it is especially emphasized that there is a serious relation between anxiety and hyperglycemia in diabetic patients (16).

Stress and anxiety in diabetic patients is a potential stimulant for chronic hyperglycemia. Major effects of stress on metabolic activity have long been demonstrated. Stress causes the secretion of a number of hormones that increase blood glucose. Moreover, it is quite difficult to control hyperglycemia triggered by stress (17).

In our study we found that there was a strong relation between severity of anxiety symptoms of those who don't know their glucose levels and the patients with high glucose levels. Measuring glucose regularly ensures the person's auto- control. In this present situation, it is possible that the increase of the anxiety symptoms in patients who have to stay at home may be the reason for not measuring blood glucose.

It was found that people with anxiety, with or without hyperglycemia, had more heart rate, skin changes. As a result of this it is thought that serious anxiety triggers the increase in plasma glucose (17). As seen in previous pandemics, isolation and quarantine can trigger anxiety and depression. Similar things have been observed in people locked in who had to be away from the people they love, personal habits and lifestyles. This situation may cause disappointment, boredom, and potential depression. Avoiding from infectious diseases may increase anxiety. This anxiety situation may increase even more with improper social avoidance guidelines and less reliable media sources (7). This situation affects blood glucose regulation in a negative way, which we found a similar result in our study.

16 % of the patients whose diabetes was regular had anxiety and 11.8 % of them were found to have severe tension and it is thought that this is in the foreground related with staying at home for a long time. It is found that patients who do not know their blood glucose levels and those with high measurements also experience severe anxiety. When compared, it is seen that the depression rate in individuals with diabetes is twice as much as in those who don't have chronic diseases (18). It is stated that the risk of developing depression in diabetic patients is about 60% (19). Depression seen in people with diabetes makes metabolic control difficult, reduces the life quality, and increases the mortality and morbidity (20). In our study, it was observed that the blood glucose level was high in 27.1% of patients with severe depressive symptoms.

In our study we found a significant deterioration in diabetes regulation of the patients with severe depressive symptoms. This situation developed with staying at home seemed to have significantly affected the blood glucose regulation.

In a study, six food categories were presented. Stress didn't affect the general intake according to these six food categories but those with emotional eating preferred sweet and high-fat food more than non-stressful people. Dietary restriction didn't seem to affect the appetite in general. Especially in emotional eaters, metabolic and weight control are affected in a negative way along with increased sugar, fatty desire to eat (20).

Again in a different study, while traditional nutrition consisting of fruit, vegetables, meat and fish was found to be associated with less depressive and anxious symptoms; nutrition with unhealthy food was found to be related with more psychological symptoms and diseases.

It is understood in this study that quality of a diet is highly related with high prevalence of mental diseases especially in chronic diseases (21). It was found in our study that patients who followed their diets had significantly low tension levels, on the other hand those who did not follow their diets had specifically high tension levels. No significant relation was detected between the diet compliance and the other mental symptoms.

In our study we also found that the relation between the diet compliance and tension was significant. From a different point of view, it is possible that the tension occurred because staying home makes it difficult to follow the diet. Therefore, in this current epidemic period, the mental situation of patients with type 2 diabetes who had to stay home causes difficulty in their compliance with diet, measurement and controlling of blood sugar. It is observed that, in order to provide positive developments in the control of the disease, visits to the patients and close follow-ups are important in this period.

Table 3. Comparison anxiety, tension, depression and excitement levels according to compliance with diet

	Not following the diet	Following the diet	Total	p
Score of anxiety symptoms (n, %)				0.651*
None	25 (19.5%)	40 (23.3%)	65 (21.7%)	
Mild	35 (27.3%)	51 (29.7%)	86 (28.7%)	
Medium severe	39 (30.5%)	51 (29.7%)	90 (30.0%)	
Severe	29 (22.7%)	30 (17.4%)	59 (19.7%)	
Score of tension symptoms (n,%)				0.017*
None	24 (18.8%)	54 (31.4%)	78 (26.0%)	
Mild	42 (32.8%)	56 (32.6%)	98 (32.7%)	
Medium severe	36 (28.1%)	45 (26.2%)	81 (27.0%)	
Severe	26 (20.3%)	17 (9.9%)	43 (14.3%)	
Score of depression symptoms (n,%)				0.292*
None	23 (18.0%)	45 (26.2%)	68 (22.7%)	
Mild	45 (35.2%)	61 (35.5%)	106 (35.3%)	
Medium severe	40 (31.3%)	41 (23.8%)	81 (27.0%)	
Severe	20 (15.6%)	25 (14.5%)	45 (15.0%)	
Score of excitement symptoms (n,%)				0.167*
None	16 (12.5%)	39 (22.7%)	55 (18.3%)	
Mild	34 (26.6%)	51 (29.7%)	85 (28.3%)	
Medium severe	41 (32.0%)	49 (28.5%)	90 (30.0%)	
Severe	37 (28.9%)	33 (19.2%)	70 (23.3%)	
Total	128 (100%)	172 (100%)	300 (100%)	

* Chi-square Test

CONCLUSION

COVID-19 pandemic has been experienced worldwide including our country. Social isolation, especially staying at home, plays an important role in order to handle the pandemic. However, the high mortality and morbidity rates of the virus cause extreme fear in humanity. Also social isolation and obligation to stay at home trigger depression and anxiety. This issue may make it more difficult to ensure metabolic control of the diseases such as tip 2 diabetes which is already difficult to manage. That's why it is of great importance to support patients mentally in this process. The necessity of continuing the follow-up and education of the patients by phone or different methods arises..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Ethic Committee (Date 18.06.2020, Decision No: 2020/279)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Overview of blood-borne viral infections in hemodialysis patients: hepatitis B, hepatitis C, human immunodeficiency virus infections

Pınar Ergen[1], Özlem Aydın[1], Ayşe Naciye Erbakan[2], Sabahat Alışır Ecder[3]

[1]İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[2]İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Department of Internal Medicine, İstanbul, Turkey
[3]İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Nephrology, İstanbul, Turkey

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ABSTRACT

Aim: This study aimed to examine the blood-borne viral infections such as hepatitis B, hepatitis C and human immunodeficiency virus (HIV) and to determine the risk factors in hemodialysis patients.

Material and Method: The datas of patients who underwent hemodialysis in the hemodialysis unit of our hospital between March 1, 2020 and March 1, 2021 were reviewed retrospectively. Their sociodemographic characteristics, habits, underlying diseases and virological indicators related to hepatitis B, hepatitis C and HIV were obtained from patient files and hospital data processing system.

Results:A total of 96 patients were included in the study. Of them, 43.8% (n=42) were female and 56.2% (n=54) were male. Their mean age was 62.61±18.11 years, ranging from 17 to 92. The duration of dialysis was less than 3 months for 46.9% (n=45) of the patients, between 3 months and 3 years for 19.8% (n=19), and 3 years and above for 33.3% (n=32). Thirty patients (31.3%) had diabetes mellitus. In addition, 1% (n=1) of the patients had HBsAg positivity, 3.1% (n=3) had anti-HCV positivity, 59.4% (n=57) had Anti- HBs positivity and 2.1% (n=2) had anti-HIV positivity. No statistically significant difference was found between the patients' HBsAg, anti-HCV and anti-HIV positivity according to gender, duration of dialysis, dialysis application site, alcohol use, surgical intervention and blood transfusion history ($p>0.05$).

Conclusion: Hemodialysis patients may be at risk for hepatitis B, hepatitis C and HIV infection if infection control guidelines are not followed strictly. In addition to complying with these guidelines, both health workers and patients should be trained constantly, patients' virological indicators should be tested regularly and hepatitis B vaccine should be administered to hemodialysis patients without seroconversion.

Keywords: Hemodialysis, HBV, HCV, HIV, seroprevalance

INTRODUCTION

Hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are pathogens that can be transmitted by blood and blood products, causing significant public health issues across the world. Hemodialysis patients with end-stage renal disease are at risk due to transmission routes of these infections.

Turkey is a medium endemic region in terms of HBV infection with an estimated HBsAg positivity of 4% (1). Studies of hemodialysis patients have reported different rates of HBsAg positivity reaching at 8.7% (2). While anti-HCV positivity is estimated to be 1% in the population, studies report this rate up to 16% in hemodialysis patients (3, 4). According to the latest data, there are a total of 25,809 HIV-infected individuals across Turkey and HIV positivity is below 0.5% in hemodialysis patients (5,6).

An evaluation of HBsAg, anti-HCV and anti-HIV positivity and Hepatitis B vaccine responses of the patients followed up in the hemodialysis unit of our hospital will guide us in following up our patients, determining relevant risk factors and developingproper prevention strategies, and also contribute to the literature on the seroprevalence of hemodialysis patients in İstanbul, Turkey.

Corresponding Author: Pınar Ergen, pergen71@hotmail.com
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MATERIAL AND METHOD

Patients followed in the hemodialysis unit of our hospital between March 1, 2020 and March 1, 2021 were included in the study. The study was approved by the Medeniyet University Göztepe Training and Research Hospital Ethics Committee (Date: 02.09.2020, Decision No: 2020/0551). The study was conducted in accordance with the Declaration of Helsinki rules. Their sociodemographic data, histories of blood transfusion and surgical intervention, vaccination status, alcohol and intravenous drug use, presence of fistula or catheter, duration of hemodialysis, and virological indicators (HBsAg, anti-HBs, anti-HBc total, anti-HCV, anti-HIV) were obtained retrospectively from patient files or hospital data processing system. Their HBsAg, anti-Delta, anti-HBs, anti-HBc total, anti-HCV and anti-HIV serology were tested using the enzyme linked immunosorbent assay (ELISA) method. Anti-HBs titer of 10 mIU/mL and above was accepted as protective antibody titer for hepatitis B. HBsAg, anti-HCV, anti-HIV positive patients were tested using HBV DNA, HCV RNA, HIV RNA test PCR (Polymerase Chain Reaction) method (Qiagen, Hilden, Germany) respectively.

Statistical Analysis

The Number Cruncher Statistical System (NCSS) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the data. Shapiro-Wilk test and graphical examinations were used to test the conformity of quantitative data to normal distribution. Mann-Whitney U test was used for comparisons between two groups of quantitative variables without normal distribution. Pearson chi-square test, Fisher's exact test and Fisher-Freeman-Halton test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 96 patients were included in the study. Their mean age was 62.61±18.11 years, ranging from 17 to 92. Of the patients, 43.8% (n=42) were female, 56.2% (n=54) were male, and %77.6 were married. The duration of dialysis was less than 3 months for 46.9% (n=45) of the patients, between 3 months and 3 years for 19.8% (n=19), and 3 years and above for 33.3% (n=32). Thirty patients (31.3%) had diabetes mellitus and five patients (5.2%) had hypertension. In addition, there were history of malignancy in 9 patients (9.3%) and polycystic kidney disease in 4 patients (4.2%).

Of the patients, 1% (n=1) had HBsAg positivity, 3.1% (n=3) had anti-HCV positivity and 2.1% (n=2) had anti-HIV positivity. The HBsAg positive patient had negative delta antibody. HBsAg, Anti-HCV, Anti-HIV positivities were all detected before starting the dialysis program. Anti-HBs positivity was observed in 59.4% (n=57) of the patients, and six (6) of them were naturally immunized. No isolated anti-HBc total positivity was observed. Anti-HBs values of six (6.3%) patients who received Hepatitis B vaccine and developed protective antibody levels were found to be negative in the following examinations.

In addition, 46.9% (n=45) of the patients were on dialysis via fistula and 53.1% (n=51) were on dialysis via catheter. Only 2.1% (n=2) of them were social drinkers, there were no patients with intravenous drug use. While 54.2% (n=52) had a history of blood transfusion, and 76% (n=73) had a history of surgical intervention.

No statistically significant difference was found between the patients' HBsAg, anti-HCV and anti-HIV positivity according to gender, duration of dialysis, dialysis application site, alcohol use, surgical intervention and blood transfusion history, and no additional risk factor was detected ($p>0.05$). **Tables 1**, **2** and **3** show the patients' HbsAg, anti-HCV and anti-HIV status and their demographic characteristics.

Table 1. Comparison of patients' HBsAg status according to their demographic characteristics

	HBsAg		p
	Negative (n=95)	Positive (n=1)	
Age			
Mean±Sd	62.62±18.21	62	
Median (Min-Max)	64 (17-92)	62 (62-62)	
Gender			[a]1.000
Male	53 (55.8)	1 (100.0)	
Female	42 (44.2)	0 (0)	
Duration of dialysis			[d]0.523
≤3 months	45 (47.4)	0 (0)	
3 months - 3 years	19 (20.0)	0 (0)	
≥3 years	31 (32.6)	1 (100.0)	
Dialysis application site			[a]0.469
Fistula	44 (46.3)	1 (100.0)	
Catheter	51 (53.7)	0 (0)	
Alcohol use	2 (2.1)	0 (0)	[a]1.000
Surgical intervention			[a]1.000
No	23 (24.2)	0 (0)	
Yes	72 (75.8)	1 (100.0)	
Blood transfusion			[a]0.458
No	43 (45.3)	1 (100.0)	
Yes	52 (54.7)	0 (0)	

[a]Fisher's Exact Test, [d]Fisher Freeman Halton Test

Table 2. Comparison of patients' anti-HCV status according to their demographic characteristics

	Anti-HCV		p
	Negative (n=93)	Positive (n=3)	
Age			
Mean±Sd	62.89±18.23	54.00±13.11	
Median (Min-Max)	64.5 (17-92)	56 (40-66)	
Gender			[a]1.000
Male	52 (55.9)	2 (66.7)	
Female	41 (44.1)	1 (33.3)	
Duration of dialysis			[d]0.201
≤3 months	45 (48.4)	0 (0)	
3 months - 3 years	18 (19.4)	1 (33.3)	
≥3 years	30 (32.3)	2 (66.7)	
Dialysis application site			[a]0.598
Fistula	43 (46.2)	2 (66.7)	
Catheter	50 (53.8)	1 (33.3)	
Alcohol use	43 (46.2)	2 (66.7)	[a]1.000
Surgical intervention			[a]1.000
No	43 (46.2)	2 (66.7)	
Yes	50 (53.8)	1 (33.3)	
Blood transfusion			[a]0.247
No	43 (46.2)	2 (66.7)	
Yes	50 (53.8)	1 (33.3)	

[a]Fisher's Exact Test, [d]Fisher Freeman Halton Test

Table 3. Comparison of patients' anti-HIV status according to theirdemographic characteristics

	Anti-HIV		p
	Negative (n=94)	Positive (n=2)	
Age			
Mean±Sd	62.80±18.22	54.00±11.31	
Median (Min-Max)	64.5 (17-92)	54 (46-62)	
Gender			[a]0.503
Male	52 (55.3)	2 (100)	
Female	42 (44.7)	0 (0)	
Duration of dialysis			[d]0.276
≤3 months	45 (47.9)	0 (0)	
3 months - 3 years	18 (19.1)	1 (50)	
≥3 years	31 (33)	1 (50)	
Dialysis application site			[a]0.217
Fistula	43 (45.7)	2 (100)	
Catheter	51 (54.3)	0 (0)	
Alcohol use	52 (55.3)	2 (100)	[a]1.000
Surgical intervention			[a]1.000
No	23 (24.5)	0 (0)	
Yes	71 (75.5)	2 (100)	
Blood transfusion			[a]1.000
No	43 (45.7)	1 (50)	
Yes	51 (54.3)	1 (50)	

[a]Fisher's Exact Test, [d]Fisher Freeman Halton Test

The only HbsAg positive patient had been receiving hepatitis B treatment for ten years and his HBV DNA was undetectable. Two patients who were positive for anti-HCV had negative HCV RNA and one of thembecame negative after antiviral treatment. The HCV RNA value of the other anti-HCV positive patient was 74.858 IU/mL. One of the anti-HIV positive patients had received HIV treatment for two years and the other for nine years. Both patients had undetectable HIV RNA levels.

There was a statistically significant relationship between anti-HBs positivity and duration of dialysis (p=0.001; p<0.01). The rate of being negative for anti-HBs was higher in the patients with dialysis duration of 3 months or less, and the rate of being positive for anti-HBs was higher in those with dialysis duration between 3 months and 3 years and those with dialysis duration of 3 years and above. The rate of being positive for anti-HBs was statistically significantly higher in the patients with fistula than in those with catheter (p=0.001; p<0.01). In addition, anti-HBs positivity was statistically significantly higher in the patients who underwent surgery than in those who did not (p=0.001; p<0.01).

Laboratory characteristics of the study patients are presented in **Table 4**.

Table 4. Laboratory characteristics of the patients

	Median (Min-Max)
Kt/V (min: 1.2)	1.5 (0.5-2.9)
WBC (4000-10.000/uL)	7.000 (2.700-49.300)
Hemoglobin (13.5-17 g/dl)	10.35 (6.1-14.5)
Plt (100.000-400.000/uL)	194.000 (48.000-513.000)
ALT(0-41 U/L)	12 (2-756)
Albumin (35-52 gr/dL)	36.5 (2-94)
Glucose (74-106 mg/dL)	103 (46-258)

Kt/V: dialyzer clerance urea. dialysis time/ volüme of distribution of urea;WBC: White blood cell; Plt: platelet; ALT: Alanine aminotransferase

DISCUSSION

It is estimated that worldwide at least 350 million people are chronically infected with HBV, 170 million with HCV and 38 million with HIV, and these infections still cause significant public health problemsacross the world (7,8). Blood is one of the most common routes of transmission of these infections. Patients with end-stage renal disease are at risk due to intravenous exposures, frequent use of blood and blood products, and frequent hospitalizations. In addition, susceptibility to infections due to impaired immune system increases, while vaccine responses decrease. Among these patients, deaths due to infections rank number two following cardiovascular diseases (9-11).

As in the world, hemodialysis is the most frequently applied renal replacement therapy (RRT) in patients with end-stage kidney disease in our country (12,13). As of the end of 2019, there are 61,341 patients in the hemodialysis program in Turkey. These patients are followed in 886 centers, 6.21% of which are hemodialysis units in university hospitals. According to the Joint Report of the Ministry of Health and the Turkish Society of Nephrology, the number of hemodialysis patients continues to increase over the years. According to the

latest data, 2.57% (n=1574) of these patients were positive for HBsAg, 3.14% (n=1928) for anti-HCV positivity, 0.43% (n= 263) for both HBsAg and anti-HCV positivity, and 0.11% (n=67) for anti-HIV positivity (13).

In our study, HBsAg positivity was found only in 1% of our patients. This low rate may be due to several reasons including Hepatitis B vaccine programs' implementation for hemodialysis patients, Hepatitis B vaccine's being added to childhood vaccines since 1998, screening of patients regularly for viral infections in accordance with the guidelines, using separate machines in isolations for HBsAg positive patients, hygiene and infection control rules' being followed by both patients and health professionals, and provision of good in-service training for health workers.

Among studies conducted with hemodialysis patients in Turkey, Sayar et al. (14) did not detect HBsAg positivity in Van province. Similarly, both Temiz et al. (15) and Yüksel et al. (16) did not detect HBsAg positivity in Diyarbakır province. However, HBsAg positivity rate was found as 0.9% by Asgin et al. (17) in Karabük province, 3.6% by Evirgen et al. in Hatay province (18), 5.5% by Çopur Çiçek et al. (4) in Rize province, 5.8% by Eser Karlıdağ et al. (19) in Elazığ province, 8.7% by Sırmatel et al. in Gaziantep province, and 0.7% by Güvenir et al. (20) in the Turkish Republic of Northern Cyprus. In our neighbors, this rate was found to be 3.2% for Iraq and 2% for Iran (21,22). In countries from different continents, the prevalence of HBV positivity was found as 2.98% for Botswana, 16.1% for Pakistan, 0% for Brazil, 12% for Kosovo, and 1.03% for Spain (21-27). As seen, the rates vary from by country and even in different geographical regions of one country.

Turkey is a country with low prevalence of HCV. This may be because intravenous drug use, which is the most important route of transmission in developed countries, is low in our country and blood donors have been tested for HCV since 1996 (3, 28, 29). Nevertheless, the rate can be higher in hemodialysis patients due to frequent parenteral interventions and lack of a protective vaccine as in Hepatitis B. In our study, HCV positivity was 3.1%, two of the patients positive for anti-HCV had negative HCV RNA, and one of them became negative after antiviral treatment. In addition, one male patient could not receive antiviral treatment due to his foreign nationality and his HCV RNA value was detectable.

Studies conducted in our country have shown that hemodialysis patients have anti-HCV positivity at rates ranging from 1.2% to 16% (2,4,14-19). Among international studies, the prevalence of anti-HCV was determined as 4.3% by Ibrahim et al. (21) in Iraq, 8.3% by Roushan et al. (22) in Iran, 43% by Telaku et al. (24) in Kosovo, and 43.2% by Lodhi et al. (26) in Pakistan. Our anti-HCV rate was close to Turkey's average.

Hemodialysis process also carries a significant risk in terms of HIV transmission. HIV transmissions originating from overseas hemodialysis units have been reported in the past years. In 1990, 33 kidney patients were infected with HIV in a dialysis center in Cordoba, Argentina, where same hemodialysis filters were used repeatedly for different patients (30). Similarly, an HIV infection outbreak was reported among 39 patients in two dialysis centers in Egypt in 1993 (31). Although similar incidents are no longer encountered, these outbreaks show how disruptions in infection control measures can cause severe health consequences.

Our study found anti-HIV positivity as 2.1%. Sayar et al. (14), Temiz et al. (15), Yüksel et al. (16), and Eser Karlıdağ et al. (19) found no anti-HIV positivity in their hemodialysis study populations. Güvenir et al. (20) reported anti-HIV positivity for only one patient (0.7%). The rate of anti-HIV positivity in our dialysis centeris higher than those reported in other Turkish studies. In the report of the Turkish Society of Nephrology published in 2019, anti-HIV positivity was determined as 0.11% for hemodialysis patients. Although Turkey is not a country with high HIV prevalence, the rates were high in our study. As we have a machine reserved for HIV-positive patients and a specific clinic to which HIV-positive individuals in our region are referred in need, which probably results in a higher frequency of HIV positive dialysis patients.

Anti-HBs positivity was observed in 59.4% (n=57) of the patients. The rate was significantly high for patients who have been on dialysis for more than 3 months. Patients in need of renal replacement therapy usually were tested and included in the vaccination program as soon as possible, preferably before starting dialysis. Six patients who were known to have antibodies against Hepatitis B before, were tested negative for Hepatitis B antibodies. Low antibody response and seroconversion may develop in patients with advanced kidney disease and their vaccine responses may be less permanent than healthy individuals. Whether a booster dose is needed for patients with end stage kidney disease should be evaluated regularly with annual anti-HBs titer checks (32, 33). It should be kept in mind that Anti-HBs titers may decrease more rapidly in these patients, and a revaccination plan should be recommended for patients without adequate antibody response (Anti-HBs < 10IU/ml) to protect them from the risk of hepatitis B infection (32, 34). A booster dose was administered to these six patients whose antibodies were found to be negative. The patients undergoing dialysis from fistula had high anti-HBs positivity. Before surgical

procedures, hepatitis B, C and HIV status are usually checked, they probably were administered a hepatitis B vaccine booster dose if needed after an antibody control before the fistula was created.

According to the annual joint reports of the Turkish Society of Nephrology, both HBsAg, anti-HCV and anti-HIV positivity have decreased over the years. Experienced health personnel, regular staff and patient training and high compliance with hygiene rules have a significant contribution to this decline. No additional risk factor that would cause HBsAg, anti-HCV, and anti-HIV positivity was encountered in our study. This was attributed to proper observance of infection control measures and careful work of healthcare professionals.

Limitation: Since this was a retrospective study, all patient data could not be reached in our study.Also our dialysis center is based in a tertiarity hospital, which may cause a selection bias and therefore our results may not reflect other dialysis centers, especially centers not affiliated with hospitals.

CONCLUSION

Hemodialysis patients may be at at an increased risk for hepatitis B, hepatitis C and HIV infection than the general population if infection control guidelines are not followed strictly. In addition to complying with these guidelines, both health workers and patients should be trained constantly, patients' virological indicators should be tested, patients should be vaccinated as soon as possible and hepatitis B vaccine should be re-administered to hemodialysis patients without seroconversion or if their antibody responses change.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medeniyet University Göztepe Training and Research Hospital Ethics Committee (Date: 02.09.2020, Decision No: 2020/0551).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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The efficiency of HALP score, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in predicting mortality in intensive care patients

Salih Kocaoğlu, Tufan Alatlı

Balıkesir University, Faculty of Medicine, Department of Emergency Medicine, Balıkesir, Turkey

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ABSTRACT

Objective: The HALP Score, which is a combination of hemoglobin, albumin, lymphocytes, and platelets, is a new index that shows nutritional status and systemic inflammation, provides information about patient prognosis. In this study, we aimed to investigate the relationship of HALP score, platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR) and with poor prognosis in intensive care patients.

Material and Method: Our study was designed retrospectively on patients admitted from the emergency department (ED) to the intensive care unit (ICU). HALP scores, PLR and NLR values were calculated from the hemoglobin, albumin, lymphocyte, platelet and neutrophil values taken from the patients within 24 hours. One-week and three-month mortality were determined as poor outcomes. The relationship between results and poor outcomes was investigated.

Results: A total of 250 patients were included in the study. The median age of the patients was 72.5%, and 43.6% (n=109) were female. When the variables between survivors and non-survivors were compared, NLR was found to be significantly higher in non-survivors. In addition, there was a significant difference between the two groups in terms of both one-week and three-month mortality regarding age, albumin, lymphocyte, and thrombocyte values. When we analyzed the diagnostic performances of HALP Score, NLR, and PLR for one-week and three-month mortality, only NLR showed significant diagnostic performance. The optimal cut-off point for NLR for both one-week and three-month mortality was 8.22 (for one-week mortality: AUC=0.598, p=0.007; for three-month mortality: AUC=0.592, p=0.011).

Conclusion: It was observed that the HALP score was not an effective parameter in predicting prognosis in intensive care patients. It is thought that NLR has a significant relationship with one-week and three-month mortality and can be used as an effective parameter in the prediction of prognosis in intensive care patients.

Keywords: Intensive care, halp score, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

This study was presented orally at the 17th National Emergency Medicine, 8th Intercontinental Emergency Medicine, 8th International Critical Care and Emergency Medicine Congress.

INTRODUCTION

Treating patients in intensive care units (ICU) and estimating mortality and morbidity has always been a challenging and critical issue for doctors. Therefore, various scoring systems have been developed for use in ICUs to predict the prognosis of patients and predict the severity of the disease (1-3). Some of the most common of these systems include Simplified Acute Physiology Score (SAPS II), Acute Physiology and Chronic Health Evaluation Score (APACHE II), Logistic Organ Dysfunction System (LODS) and Mortality Probability Model (MPM II). However, no consensus has yet been reached on which scoring system is the best for the discrimination of critically ill patients (2,4). The ideal scoring system should reveal the patient's prognosis best, and it should be easy to calculate.

General nutritional status, presence of inflammation, and susceptibility to atherosclerosis are important causes of mortality and prognosis in intensive care patients. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are valuable prognostic parameters that indicate the patient's overall immune strength against various stress factors and are used in the prognostic evaluation of several diseases, including community-acquired pneumonia, malignancies, acute pulmonary embolism, and myocardial infarction (5,6). In addition, recently, there are studies showing that an index

Corresponding Author: Salih Kocaoğlu, salihkocaoglu1986@gmail.com
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called hemoglobin, albumin, lymphocyte, platelet (HALP) score reflects the general nutritional status and systemic inflammation of the patients. This score has been proven to be a useful prognostic factor in stomach, prostate, bladder and kidney malignancies and patients with an acute ischemic attack (7-11). Lymphocytes play a key regulatory role in inflammation. Platelet hyperactivity increases the risk for thromboembolism, atherosclerotic lesions and may cause abnormal thrombosis that exacerbates the inflammatory response (12). Hypoalbuminemia and anemia are indicators of malnutrition.

In this study, we investigated the prognostic role of HALP score, PLR, NLR and in patients admitted from the emergency department to the ICU.

MATERIAL AND METHOD

A retrospective design was used in the study, and it was approved by Balıkesir University Clinical Researchs Ethics Committee (Date: 08.09.2021, Decision No: 2021/182). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study consisted of 250 patients who presented to Balıkesir University Faculty of Medicine Emergency Service for various reasons between January 2020 and May 2021 and were later admitted to the ICU. All patients over the age of 18 who presented to the emergency department as an outpatient or were brought by ambulance and were admitted to the ICU after the examination and follow-up were included in the study without any exclusion criteria. Patients who had missing laboratory data and were referred to an external center during their follow-up were excluded from the study. Blood counts were analyzed using an autoanalyzer (Beckman Coulter Hematology Analyzer LH780). All serum biochemical parameters were tested using an automated biochemical analyzer (Beckman Coulter Chemistry Analyzer AU680). Hemoglobin, albumin, lymphocyte, platelet, and neutrophil values of the patients taken within 24 hours were analyzed. HALP score and NLR and PLR values were calculated based on these values. HALP score was calculated using the following formula: hemoglobin (g/L) × albumin (g/L) levels × lymphocyte count (/L)/platelet count (/L) (7,8,13). NLR was obtained by dividing the neutrophil count by the lymphocyte count, and PLR was obtained by dividing the platelet count by the lymphocyte count. Poor outcomes were considered as our patients' one-week or three-month mortality.

Statistical Analyses

Shapiro-Wilk test was used to test the normality of variables. Continuous variables with normal distribution were expressed as mean ± standard deviation, and comparisons between two independent groups were performed with independent samples t-test. Non-normal variables were expressed as median (minimum-maximum) values, and comparisons between two independent groups were performed with the Mann-Whitney U test. Receiver operating characteristics (ROC) curve analysis was performed to evaluate and compare the performances of diagnostic markers. Youden J index was used to obtain an optimal cut-off value, and related sensitivity, specificity, positive predictive, and negative predictive values were given. Binary logistic regression analysis was performed to detect the risk factors for in-hospital mortality. The significance level was taken as $\alpha = 0.05$. Two-tailed hypothesis tests were used. Statistical analyses were performed with IBM SPSS Statistics version 23.0 (IBM Corp., USA) and MEDCALC VERSION 12.3.0.0.

RESULTS

250 patients were included in our analysis. The median age of the patients was 72.50 (min-max: 25.00-96.00) years, and 43.60% (n=109) of them were female. One-week and three-month mortality rates were 34.40% (n=86) and 55.60% (n=139), respectively. When we compared the variables between survivals and non-survivals, NLR was significantly lower in the survival group than the non-survival group, both for one-week and three-month mortality. Also, there was a significant difference in terms of age, albumin, lymphocytes, and platelets between the two groups, both for one-week and three-month mortality (**Table 1, Table 2, Figure 1**).

Table 1. Comparison of patient characteristics in terms of one-week mortality

Variables	Survivor	Non-survivor	p value
Patients, n	164	86	-
Age (yr)[&]	72.00 (25.00-96.00)	75.00 (44.00-94.00)	**0.037**
Gender[#]			0.686
female	70 (42.68)	39 (45.34)	
male	94 (57.31)	47 (54.65)	
Neutrophils (10^9/L)[&]	9.35 (0.20-25.00)	10.50 (1.10-28.30)	0.347
Albumin (g/L)*	31.70±5.97	29.73±6.06	**0.014**
Hemoglobin (g/L)*	120.92±21.20	121.09±20.66	0.951
Lymphocytes (10^9/L)[&]	0.70 (0.10-42.30)	0.60 (0.10-7.80)	**0.008**
Platelets (10^9/L)[&]	263.00 (37.00-1205.00)	219.00 (40.00-589.00)	**<0.001**
HALP score[&]	10.65 (0.98-328.87)	10.57 (0.00-86.92)	0.380
NLR[&]	11.22 (0.25-135.00)	14.17 (1.92-82.00)	**0.011**
PLR[&]	335.00 (6.71-3012.50)	324.00 (32.50-1796.67)	0.706

Data given as *mean±standard deviation, &median (minimum-maximum) or #n (%)

Table 2. Comparison of patient characteristics in terms of three-month mortality

Variables	Survivor	Non-survivor	p value
Patients, n	111	139	-
Age (yr)[&]	71.00 (25.00-96.00)	75.00 (44.00-94.00)	**0.005**
Gender[#]			0.877
female	49 (44.14)	60 (43.17)	
male	62 (55.86)	79 (56.83)	
Neutrophils (10^9/L)[&]	9.30 (0.20-19.30)	9.70 (1.10-28.30)	0.223
Albumin (g/L)*	32.72±5.54	29.67±6.13	**<0.001**
Hemoglobin (g/L)*	122.06±21.61	120.11±20.49	0.467
Lymphocytes (10^9/L)[&]	0.70 (0.10-42.30)	0.60 (0.10-7.80)	**0.041**
Platelets (10^9/L)[&]	264.00 (76.00-1205.00)	236.00 (37.00-719.00)	**0.004**
HALP score[&]	10.51 (0.98-328.87)	10.71 (0.00-86.92)	0.223
NLR[&]	11.00 (0.25-135.00)	14.36 (1.92-83.33)	**0.012**
PLR[&]	340.91 (6.71-3012.50)	322.83 (32.50-2000.00)	0.774

Data given as *mean±standard deviation, &median (minimum-maximum) or #n (%)

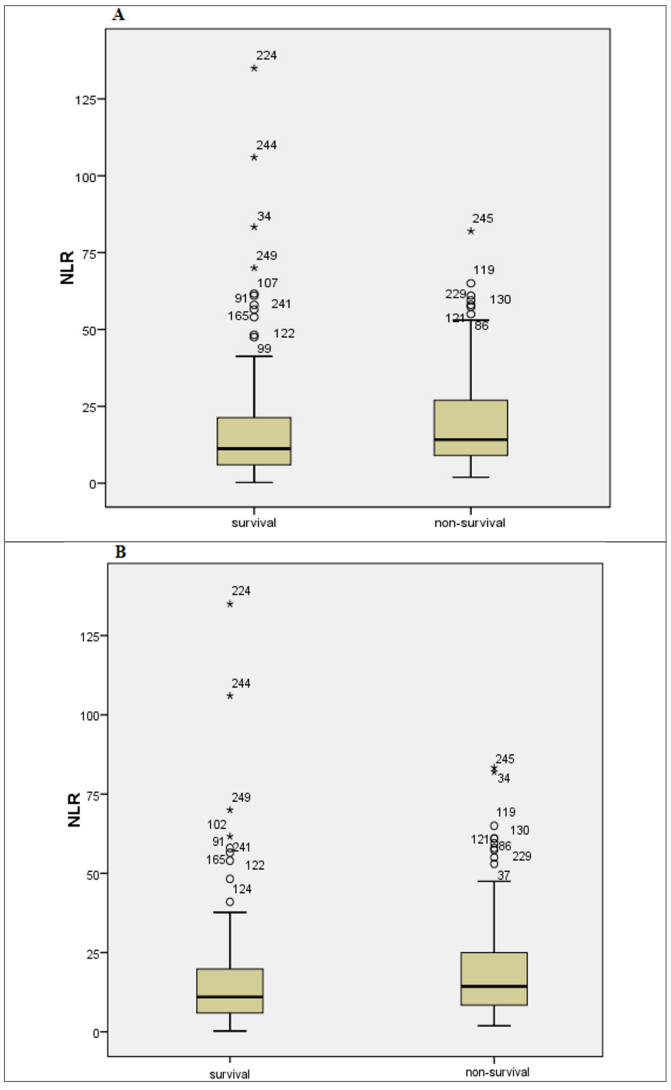

Figure 1. Box-plots for NLR in **A)** one-week survivals and non-survivals, **B)** three-month survivals and non-survivals. Outliers and extreme values are marked with ° and *, respectively.

When we examined the diagnostic performances of HALP score, NLR, and PLR for one-week and three-month mortality, only NLR showed a significant diagnostic performance. Optimal cut-off value was 8.22 for NLR both for one-week and three-months mortality (for one-week mortality: AUC=0.598, p=0.007; for three-month mortality: AUC=0.592, p=0.011) (**Table 3, Table 4**).

Table 3. ROC curve analysis results for HALP score, NLR, and PLR

	Accuracy index	HALP score	NLR	PLR
One-week mortality	AUC	0.534	0.598	0.515
	p-value	0.383	0.007	0.704
	Cut-off value	≤6.02	>8.22	>165.56
	Youden J index	0.093	0.201	0.072
	Sensitivity (95% CI)	32.56 (22.80-43.50)	82.35 (72.60-89.80)	85.88 (76.60-92.50)
	Specificity (95% CI)	76.83 (69.60-83.10)	37.80 (30.40-45.70)	21.34 (15.30-28.40)
Three-month mortality	AUC	0.545	0.592	0.511
	p-value	0.222	0.011	0.774
	Cut-off value	≤6.03	>8.22	>780
	Youden J index	0.125	0.157	0.105
	Sensitivity (95% CI)	32.37 (24.70-40.80)	76.09 (68.10-82.90)	19.57 (13.30-27.20)
	Specificity (95% CI)	80.18 (71.50-87.10)	39.64 (30.50-49.40)	90.99 (84.10-95.60)

AUC: Area under the curve, CI: Confidence interval

We performed binary logistic regression analysis with the backward conditional method by entering the significant variables and gender into the model to predict both one-week and three-month mortality, respectively. NLR was added to the model after it was categorized according to its optimal cut-off value obtained from ROC curve analysis. In the first model (p<0.001 for Omnibus test), age, albumin, platelets, and NLR (>8.22/≤8.22) were the remaining variables. Platelets and NLR were found to be statistically significant risk factors for one-week mortality. An NLR value of >8.22 increased the risk for one-week mortality 2.568 times, whereas a one-unit increase in the platelets level decreased the risk for one-week mortality 0.996 times.

In the second model (p<0.001 for Omnibus test), age, albumin, platelets, and NLR (>8.22/≤8.22) were the remaining variables. Age, albumin, platelets, and NLR were found to be statistically significant risk factors for three-month mortality. An NLR value of >8.22 increased the risk for three-month mortality 1.823 times, whereas a one-unit increase in age increased the risk for three-month mortality 1.032 times, a one-unit increase in albumin level decreased the risk for three-month mortality 0.924 times, and a one-unit increase in platelets level decreased the risk for three-month mortality 0.998 times (**Table 4**).

Table 4. Results of logistic regression analyses

Variables	One-week outcome				Three-month outcome			
	p value	OR	95% CI for OR		p value	OR	95% CI for OR	
			Lower	Upper			Lower	Upper
Age	0.082	1.021	0.997	1.044	0.004	1.032	1.010	1.055
Albumin	0.097	0.960	0.915	1.007	0.001	0.924	0.881	0.970
Platelets	0.002	0.996	0.993	0.998	0.045	0.998	0.996	1.000
NLR (RC: ≤8.22)	0.005	2.568	1.323	4.982	0.041	1.823	1.024	3.248

OR: Odds ratio, CI: Confidence interval, RC: Reference category

DISCUSSION

In this study, we examined the prognostic prediction of HALP score in intensive care patients. HALP score is a new index that combines hemoglobin, albumin levels with lymphocyte and thrombocyte counts and has been recently reported to show prognosis in various cancer and stroke patients. No significant relationship was found between HALP score and the prognosis of intensive care patients in our study, but a significant relationship was found between albumin, lymphocyte, and platelet values and mortality when the values were examined individually. Regarding HALP score and NLR and PLR values in our study, only NLR was found to be associated with one-week and three-month mortality.

ICUs are hospital units that have a high mortality rate, where critically ill patients are hospitalized. In some studies in the literature, various intensive care mortality rates have been reported (Karagöz et al. (14), 44.7%; Altaş et al. (15), 57%; Kutlucan et al. (16), 46.8%). Similar to the literature, in our study, too, one-week and three-month mortality rates were found to be 34.4% and 55.6%, respectively. Age is one of the important factors affecting the prognosis in intensive care patients. It is known that advanced age is closely associated with mortality in intensive care patients (14,16). We also found the mean age of non-surviving patients to be significantly higher than those who survived.

HALP score is a newly defined, valuable index that shows the patient's systemic inflammation and nutritional status. In this index, the general well-being of the patient is assessed based on hemoglobin, albumin, lymphocyte, and platelet values. A high HALP score is associated with longer survival (8,11,13). Anemia is a common condition in intensive care patients. The relationship between low hemoglobin levels and low quality of life has been demonstrated in randomized controlled studies (17). Serum albumin has often been used to assess nutritional status and visceral protein synthesis. Lymphocytes play a key role in inflammation. Excess platelet and hyperactivity can lead to thromboembolism and atherosclerotic lesions. HALP score, which is used to evaluate all these factors together, can give us important information about the prognosis of the patient. Peng et al. (18) showed a significant correlation between HALP score and survival in patients with bladder cancer. Feng et al. (19) stated that HALP score was an independent prognostic index in patients with esophageal cancer. Tian et al. (11) showed that HALP score was associated with 90-day and 1-year mortality in patients with stroke. Xu et al. (13) stated that HALP score was a good predictor of postoperative survival and recurrence in patients with pancreatic cancer. However, in our study, unlike the literature, HALP score did not yield significant results in terms of prognosis in intensive care patients. High albumin and lymphocyte levels showed a significant relationship with survival. However, high levels of platelet were observed in patients who survived, while low platelet levels were expected according to the HALP score. We think that we obtained an insignificant HALP score due to this situation.

PLR is recognized as a new marker in many systemic inflammatory diseases (20). PLR and NLR are indicators of the general immune response to various stress stimuli and play an important role in the prognostic assessment of a number of diseases, including community-acquired pneumonia, malignancies and myocardial infarction (5,6). Altaş et al. (15) showed that high PLR was associated with mortality in patients hospitalized in the ICU with the diagnosis of pneumonia. In addition to these, Yea et al. (21) showed that the PLR value was a significant marker for mortality in chronic obstructive pulmonary disease. However, in their study on patients with sepsis, Bıyıklı et al. (22) found no significant relationship between PLR and mortality. Although PLR is a low-cost, easy-to-use marker in intensive care conditions, similar to the Bıyıklı et al. (22), no significant relationship was found between PLR and mortality in our study, either.

NLR is an inflammatory biomarker that can be used as an indicator of systemic inflammation. It is obtained with a simple method using laboratory tests routinely performed in the hospital without additional cost. NLR has been shown to be closely associated with mortality and prognosis in many diseases (23). Gharebaghi et al. (24) (in ICU patients with sepsis), Liu et al. (25) (in sepsis patients), and King et al. (25) (in COVID-19 patients) showed that NLR was an effective marker. Altas et al. (15) reported 81.3% sensitivity, 77.1% specificity, and 11.3% cutoff value for NLR and stated that it was a good

parameter in the estimation of mortality in intensive care patients. Consistent with the literature, in our study, too, a significant correlation was found between NLR value and one-week and three-month mortality. Optimal cut-off value was 8.22 for NLR both for one-week and three-months mortality and the values were found as AUC=0.598, p=0.007 for one-week mortality and AUC=0.592, p=0.011 for three-month mortality.

CONCLUSION

The HALP score and PLR value were not found to be good predictors of prognosis in intensive care patients. It is thought that NLR has a significant relationship with one-week and three-month mortality and can be used as an effective parameter in the prediction of prognosis in intensive care patients.

Limitations

Since our study was retrospective and data were obtained from patients treated with a single treatment modality, our results may have a selection bias. Our data sample was small. Patients who were referred to an external center were excluded from the study as their mortality could not be determined. Therefore, these limitations could potentially limit the accuracy of our results. We think that our study should be supported by additional prospective, multicenter studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Clinical Researchs Ethics Committee (Date: 08.09.2021, Decision No: 2021/182).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Evaluation of knowledge levels about dental trauma (avulsion) and treatment approach of the students of medicine and dentistry faculties

Simge Gümüş, Elif Pınar Bakır

Dicle University, Faculty of Dentistry, Department of Restorative Dentistry, Diyarbakır, Turkey

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ABSTRACT

Aim: In this study aimed to evaluate the knowledge of 4th and 5th grade students of Dicle University Faculty of Medicine and Dentistry and their approach to first intervention in the face of avulsion, which is the one of the types of dentoalveolar injuries.

Material and Method: 300 students selected by random sampling method among 4th and 5th grade students of Dicle University Faculty of Medicine and Dentistry. 17 questions and a questionnaire consisting of three parts were applied to the total of three hundred students from two faculties. The data obtained in this study were analyzed with IBM SPSS 21 package program. While interpreting the results, 0.05 was used as the significance level.

Results: There is a statistically significant relationship between the faculty and the previous trauma/emergency or first aid course status ($p < 0.05$). While 34% of the medical school and 86.67% of the dental students had not taken a trauma/emergency or first aid course before, 66% of the medicine faculty and 13.33% of the dentistry faculty have previously taken a trauma/emergency or first aid course. There is a statistically significant correlation between gender and previous trauma/emergency or first aid course status ($p < 0.05$). While 76.64% of women and 51.3% of men had not taken traum /emergency or first aid courses before; 23.36% of women and 48.7% of men have previously received a trauma/emergency or first aid course.

Conclusion: According to this study, it is thought that the medical and dental faculty students who came to the clinical stage of their education had insufficient knowledge about dental trauma, so it would be appropriate to provide dental health information with more comprehensive and understandable way in the education curriculum of the faculties. It will be appropriate to give interdisciplinary seminars, case presentations and lectures on practical emergency response on dental trauma.

Keywords: Dental trauma; avulsion; emergency intervention

INTRODUCTION

Dentoalveolar injuries are considered among the more common traumas, especially in children (1). A literature review from 1995 to 2007 shows that the rates of traumatic dental injury in deciduous and permanent teeth are high worldwide (2). Statistics obtained through independent studies planned in various countries show that one fourth of all school children and almost one third of adults experience trauma related to permanent teeth (3). Although the most common cause is falling, sports, collisions, physical leisure activities, striking an object and traffic accidents are the main causes of traumatic dental injuries (4-6). Data obtained from clinical studies show that the permanent upper central teeth are most frequently affected by dentoalveolar injuries, followed by the upper lateral teeth (7).

Among the dentoalveolar traumas, avulsion has the most severe prognosis. It is defined as the complete separation of the tooth from the alveolar socket due to trauma and it is a serious disorder that constitutes 7.6% of traumatic dental injuries (8). Avulsion is a complicated type of trauma that affects the periodontal ligaments and alveolar socket as well as affecting the pulp of the tooth (9). The most common period of this type of trauma, which can be encountered regardless of age; It has been recorded in the age range of 8-12 in permanent teeth. The low resistance of periodontal ligaments against incoming extruding forces is explained as the most important reason for the frequency in this age range (10). Following avulsion cases, possible anterior tooth loss in this age group may cause serious psycho-social trauma, functional and aesthetic impairment in children and reduce the quality of life of the individual (11).

Corresponding Author: Simge Gümüş, dtsimgegumus@gmail.com
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Immediate intervention in avulsion teeth should be done as soon as possible, because the vitality of the tooth and the prognosis of the treatment depend on how the avulsed tooth was handled during first aid and intervention procedures at the time of the accident (12). The prognosis of the tooth and the success of the treatment may vary according to the time spent outside the socket after trauma, where and under what conditions the avulsed tooth is kept, the contamination status, the root development stage of the tooth, the age and systemic status of the individual (13). Fast and appropriate emergency response to avulsion teeth, especially in young children; is very important in terms of ideal long-term prognosis (14). The time spent outside the socket is of great importance for the viability of periodontal ligament cells. Therefore, the ideal emergency response; replanting the avulse into the female socket as soon as possible in the correct form and angle (15). Another issue critical to the vitality of periodontal ligament cells is the environment in which the avulsed tooth is transplanted for treatment. In order to prevent dehydration of the periodontal ligaments, it should be transplanted with solutions such as saline, milk and saliva with appropriate osmolarity and correct pH value (16). In up-to-date research on suitable transport solutions, HBSS (Hank's Balanced Salt Solution); It has been reported that periodontal ligament cells are viable for up to 72 hours with ideal pH and appropriate osmolarity, and it is the ideal transport solution that can be used due to these properties (17). Studies on solutions containing current herbal medicaments such as propolis, coconut water and mulberry juice also take place in the literature. Yet, although no evidence of use in Turkey, kits designed specifically for the transport of foreign origin research (Dentosafe®, Dentosaf GmbH, Medica, Iserlohn, Germany; EMT Tooth Saveur, I smartpractice. co, Phoenix, AZ, USA) is used and that special It has been reported that the kits preserve cell viability for up to 48 hours and then functional improvement is observed in the teeth (18). Although the milk teeth can be replanted like permanent teeth; In practice, it is not preferred frequently due to the possibility of damage to the permanent tooth germ.

When it comes to the replantation stage in the treatment of avulsed teeth, it is first necessary to remove the foreign materials on the root surface and the blood clot in the socket by washing with water, serum or sterile saline without applying pressure. Following replantation, it should be fixed with a flexible splint for 2 weeks; Afterwards, the patient should be given tetanus vaccine for prophylaxis and systemic antibiotic treatment should be initiated (19, 20, 21). In avulsion teeth that have completed root development, root canal treatment should be started within 2 weeks after replantation (22).

In teeth with unclosed apex brought in short time and suitable storage conditions; In order to allow revascularization, root canal treatment should not be performed at the first stage, and in case of clinical infection, necrosis or pathological resorption, apexification should be initiated (23). In addition, systemic antibiotics and tetanus vaccine should be administered to the patient (20,21).

In studies conducted in many different countries, the level of awareness and knowledge of dental trauma, especially avulsion, of dentists and non-dentists have been questioned. These studies; Primary school teachers, especially parents, focused on occupational groups that frequently interact with children, such as school nurses, and showed that these groups' awareness and knowledge about dental traumas were insufficient (24-27). Although primary school teachers and parents frequently encounter avulsion, health professionals who intervene and treat avulsion teeth are dentists or emergency service workers. In a similar study conducted in Chile, it was reported that the first place to intervene in traumatic dental injury cases was the hospital emergency services due to the fact that dental clinics working during working hours are not accessible outside of working hours (28). For this reason, it is of critical importance to evaluate the knowledge level and approach of medical physicians who are likely to be applied for the first time in trauma cases. The aim of this study is; To determine the knowledge levels and approaches of the students of Dicle University Faculty of Medicine and Dentistry about traumatic dental injuries.

MATERIAL AND METHOD

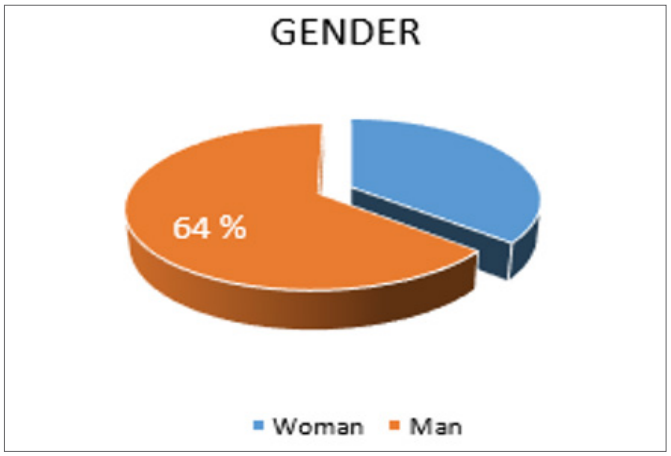
Ethical approval of the study was obtained from Dicle University Faculty of Dentistry Ethics Committee (Date: 27.11.2019, Decision No: 2019/48). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

4th and 5th grade students who continue their education at Dicle University Faculty of Medicine and Dentistry during the 2019-2020 academic year were included in the study. While 150 of the participating students were chosen from the medicine faculty; 150 of them were chosen from the dentistry faculty. Before the questionnaires were applied, the purpose and scope of the study were explained to the participants and their informed consents were obtained; Surveys were then distributed. Data collection forms were distributed to participants who accepted the study and were asked to answer them. The data collection form consists of 17 questions and 3 parts, whose validity and reliability have been tested and used in a similar study published in the literature on the level of knowledge and awareness in the emergency treatment of dental injuries. In the

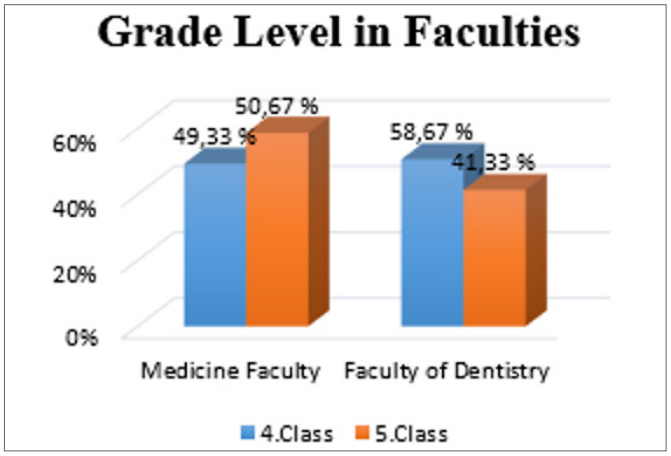
first part, the personal information of the participant student was questioned, in the second part, his personal experiences in the face of the situation, and in the third part, his attitudes towards avulsion. The questionnaires were filled out and delivered to us on the same day. In the study, one-to-one face-to-face interview technique was applied. Each participant answered the questionnaire separately. The data obtained in this study were analyzed with IBM SPSS 21 package program. While examining the relationships between groups of nominal variables, Chi-Square analysis was applied. Fisher's Exact Test was used in cases where the expected values in the cells in 2x2 tables did not have sufficient volume, and Pearson's Chi-Square analysis was applied with the help of Monte Carlo Simulation in RxC tables. While interpreting the results, 0.05 was used as the significance level; It was stated that there is a significant relationship when p <0.05, and there is no significant relationship when p> 0.05.

RESULTS

The rates regarding gender, faculty and class information of the participants included in the study are shown in **Graph 1** and **2** below.



Graph 1. Gender distribution plot



Graph 2. Distribution of regarding grade levels in faculties

The rate of those who previously received trauma/emergency or first aid course was 39.67%, and the rate of those who did not take a course was 60.33%. The rate of those who have seen tooth injury before is 69%. The rate of those who encounter broken tooth trauma is 66.67%. The rate of occurrence of traumas as a result of falling is 42.51%. Participants in the study stated that when such a situation is encountered, the most appropriate approach is to stop the bleeding at 42% and search for the tooth.

The appropriate time to get professional help is 39% 30 minutes. As stated within. The first place to apply for treatment was stated as the faculty of dentistry at a rate of 39.67%. It is stated that if the dislocated tooth is dirty, it will be cleaned by keeping it under tap water for a few seconds without rubbing 56.33%. It has been stated that the dislocated tooth will be held by 68% of its visible surface and will be preserved in 28.67% milk environment. The rate of those who can replace the tooth that has been displaced is 45.67%. It is important that 82% of the tooth that comes out is a milk tooth. The rate of those who can distinguish between milk teeth and permanent teeth is 69%. It was stated that 88.33% of the milk tooth should not be replaced when it is dislodged

The data obtained in 6 of the questions included in the questionnaire gave statistically significant results with the gender variable (p <0.05). While 76.6% of the female participants reported that they had received a trauma/emergency or first aid course before, 51.3% of the male participants reported that they took this course. While 61.7% of women answered "yes" to the question in which the condition of seeing tooth injury was questioned before, this rate was reported as 73.1% for men. While the rate of female participants who stated that the trauma occurred as a result of falling was 57.6%, the rate of male participants remained at 35.5%. 50.5% of women and 33.7% of men stated that the first place to apply for treatment is the faculty of dentistry. While 43% of the women gave the appropriate answer to the question of the environment where the removed tooth will be preserved, the same response rate for men remained at 20.8%. 78.5% of the female participants stated that they could distinguish between the milk female and the permanent female, while 63.8% of the male participants stated that they could distinguish them.

Considering the faculty variable, the data obtained from 13 questions were found to be statistically significant. 66% of medical faculty students answered "yes" to the question of "Have you ever taken a trauma/emergency or first aid course?", While this rate remained at 13.3% for dental students. While 74.5% of medical faculty

students and 57.7% of dental students faced with broken teeth trauma, 36.3% of medical students and 49.5% of dental students stated that trauma occurred as a result of falling. 57.3% of the medical faculty stated that the most appropriate approach when faced with such a situation is to stop the bleeding and search for the tooth, while this rate remained at 26.7% in the dental faculty. 29.33% of the Faculty of Medicine and 48.67% of the Faculty of Dentistry, 30 minutes of the appropriate time to get professional help. stated that it was inside. While 30.7% of the participants from the medical faculty chose the faculty of dentistry as the first place to apply for treatment, this rate was reported as 48.7% for the participants from the Faculty of dentistry.

In the case that the tooth that comes out is dirty; 36% of the medical faculty and 76.7% of the dentistry faculty stated that they would keep it under tap water for a few seconds without scrubbing, while 59.3% of the medical faculty students and 76.7% of the dentistry students stated that the displaced tooth was correct. While 52% of the dentistry faculty gave the answer to the question

Table 1. Analysis results of the relationship between gender and variables

	Gender						Ki-kare tests	
	Women		Man		Total			
	n	%	n	%	n	%	Ki-kare	p
Have you ever taken a trauma/emergencies or first aid course?							18.47	0.001
Yes	25	23.36	94	48.7	116	39.67		
No	82	76.64	99	51.3	181	60.33		
Total	107	100	193	100	300	100		
Have you ever seen a dental injury before?							4.164	0.041
Yes	66	61.68	141	73.06	207	69		
No	41	38.32	52	26.94	93	31		
Total	107	100	193	100	300	100		
What kind of trauma did you encounter?							*	1
Broken tooth	44	66.67	94	66.67	138	66.67		
Barely displaced tooth in the mouth	6	9.09	13	9.22	19	9.18		
Totth out of its socket	15	22.73	33	23.4	48	23.19		
Other	1	1.52	1	0.71	2	0.97		
Total	66	100	141	100	207	100		
State the reason for the trauma							*	0.003
Sports accident result	10	15.15	51	36.17	61	29.47		
Violence (fighting, child abuse)	10	15.15	31	21.99	41	19.81		
Fall result	38	57.58	50	35.46	88	42.51		
As a result of a traffic accident	6	9.09	8	5.67	14	6.76		
Other	2	3.03	1	0.71	3	1.45		
Total	66	100	141	100	207	100		
What would be the most appropriate approach if you encounter such a situtation?							7.368	0.061
Stop bleeding	24	22.43	52	26.94	76	25.33		
Stopping bleeding and looking for a tooth	38	35.51	88	45.6	126	42		
Calling the female and calling for help	12	11.21	18	9.33	30	10		
Searching for the female and after finding it, replacing the casualty's tooth	33	30.84	35	18.13	68	22.67		
Total	107	100	193	100	300	100		
How long do you think it is appropriate to seek professional help?							5.628	0.229
Now	20	18.69	35	18.13	55	18.33		
In 30 minutes	49	45.79	68	35.23	117	39		
In a few hours	30	28.06	66	34.2	96	32		
Within the first 24 hours	6	5.61	22	11.4	28	9.33		
No need for professional help	2	1.87	2	1.04	4	1.33		
Total	107	100	193	100	300	100		
Where would you go to first place for treatment?							22.058	0.001
No treatment needed	2	1.87	1	0.52	3	1		
Any hospital	17	15.89	54	27.98	71	23.67		
Faculty of dentistry	54	50.47	65	33.68	119	39.67		
Dentist's office	21	19.63	20	10.36	41	13.67		
Oral and dental health center	13	12.15	53	27.46	66	22		
Total	107	100	193	100	300	100		

of the environment in which the removed tooth will be preserved, this rate was calculated as only 5.3% in the medical faculty. While 15.3% of the medical faculty and 76% of the dentistry faculty stated that they can replace the tooth that has been displaced, 74% of the medical school and 90% of the dentistry faculty stated that it is important that the tooth is a milk tooth. While 99.33% of the dentistry faculty answered yes to the question we question the distinction between primary teeth and permanent teeth, this rate remained at 38.7% in the medical faculty. When the milk tooth is displaced, 95.3% of the medical school and 81.3% of the dentistry faculty think that the tooth should be replaced.

Statistically significant data were obtained on the class variable in 8 questions in the content of the questionnaire. While 75.3% of the 4th grade students and 61.6% of the 5th graders reported having a tooth injury before, 50.8% of the 4th grade students and 30.6% of the 5th grade students reported trauma as a result of falling. In case of tooth dislocation, 31.5% of 4th grade students answered the question of the most appropriate approach to stop bleeding and search for the tooth, while the rate for 5th grade students was calculated as 54.35%. 40.1% of 4th grade students and 37.7% of 5th grade students are eligible for professional help. While the rate of 4th grade students who think that the place to apply for treatment is dentistry, 48.8%, the rate of 5th grade students remained at 29%. 59.3% of the 4th grade and 52.9% of those in the 5th grade, to the question asked about the cleanliness of the dislodged tooth if it is dirty, answered that if the removed tooth is dirty, it will keep it under tap water for a few seconds without rubbing. While 78.4% of the displaced females in the 4th grade stated that 55.8% of the 5th grade students would hold the visible surface, the displaced females were replaced by 46.9% of the 4th grade and 63% of the 5th grade students.

Table 2. Analysis results of the relationship between the faculties and the variables

	Faculty						Ki kare tests	
	Medicine		Dentsitry		Total			
	n	%	n	%	n	%	Ki kare	p
How do you keep the tooth coming out?							19.658	0.001
From the root zone	11	7.33	17	11.33	28	9.33		
From the visible surface	89	59.33	115	76.67	204	68		
I don't think it matters	50	33.33	18	12	68	22.67		
Total	150	100	150	100	300	100		
In which environment do you keep the tooth that has been displaced?							156.843	0.001
Tap water	17	11.33	0	0	17	5.67		
Alcohol	11	7.33	3	2	14	4.67		
Ice	22	14.67	0	0	22	7.33		
Sterile solution	35	23.33	38	25.33	73	24.33		
Milk	8	5.33	78	52	86	28.67		
In the mouth	6	4	24	16	30	10		
Salive	11	7.33	3	2	14	4.67		
Dry environment	8	5.33	0	0	8	2.67		
Other	1	0.67	4	2.67	5	1.67		
Don't know	31	20.67	0	0	31	10.33		
Total	150	100	150	100	300	100		
Con you replace a dislocated tooth?							111.249	0.001
Yes	23	15.33	114	76	137	45.67		
No	127	84.67	36	24	163	54.33		
Total	150	100	150	100	300	100		
Do you think it is important that the tooth that comes out is a milk tooth?							13.008	0.001
Yes	111	74	135	90	246	82		
No	39	26	15	10	54	18		
Total	150	100	150	100	300	100		
Can you distinguish between primary teeth and permanent teeth?							129.048	0.001
Yes	58	38.67	149	99.33	207	69		
No	92	61.33	1	0.67	93	31		
Total	150	100	150	100	300	100		
Should the milk tooth be placed in its place when it comes out?							14.264	0.001
Yes	7	4.67	28	18.67	35	11.67		
No	143	95.33	122	81.33	265	88.33		
Total	150	100	150	100	300	100		

Table 3. Analysis results on the relationship between classes and variables

	Class						Ki-kare tests	
	4th class		5th class		Total			
	n	%	n	%	n	%	Ki-kare	p
Have you ever taken a trauma/emergencies or first aid course?							0.286	0.593
Yes	62	38.27	57	41.3	119	39.67		
No	100	61.73	81	58.7	181	60.33		
Total	162	100	138	100	300	100		
Have you ever seen a dental injury before?							6.553	0.01
Yes	122	75.31	85	61.59	207	69		
No	40	24.69	53	38.41	93	31		
Total	162	100	138	100	300	100		
What kind of trauma did you encounter?							*	0.543
Broken tooth	84	68.85	54	63.53	138	66.67		
Barely displaced tooth in the mouth	10	8.2	9	10.59	19	9.18		
Tooth out of its socket	26	21.31	22	25.88	48	23.19		
Other	2	1.64	0	0	2	0.97		
Total	122	100	85	100	207	100		
State the reason for the trauma							20.319	0.001
Sports accident result	27	22.13	34	40	61	29.47		
Violence (fighting, child abuse)	18	14.75	23	27.06	41	19.81		
Fall result	62	50.82	26	30.59	88	42.51		
As a result of a traffic accident	12	9.84	2	2.35	14	6.76		
Other	3	2.46	0	0	3	1.45		
Total	122	100	85	100	207	100		
What would be the most appropriate approach if you encounter such a situtation?							46.173	0.001
Stop bleeding	36	22.22	40	28.99	76	25.33		
Stopping bleeding and looking for a tooth	51	31.48	75	54.35	126	42		
Calling the female and calling for help	14	8.64	16	11.59	30	10		
Searching for the female and after finding it, replacing the casualty's tooth	61	37.65	7	5.07	68	22.67		
Total	162	100	138	100	300	100		
How long do you think it is appropriate to seek professional help?							11.186	0.025
Now	38	23.46	17	12.32	55	18.33		
In 30 minutes	65	40.12	52	37.68	117	39		
In a few hours	48	29.63	48	34.78	96	32		
Within the first 24 hours	9	5.56	19	13.77	28	9.33		
No need for professional help	2	1.23	2	1.45	4	1.33		
Total	162	100	138	100	300	100		
Where would you go to first place for treatment?							20.691	0.001
No treatment needed	1	0.62	2	1.45	3	1		
Any hospital	33	20.37	38	27.54	71	23.67		
Faculty of dentistry	79	48.77	40	28.99	119	39.67		
Dentist's office	26	16.05	15	10.87	41	13.67		
Oral and dental health center	23	14.2	43	32.16	66	22		
Total	162	100	138	100	300	100		

DISCUSSION

Dentoalveolar injuries, which are the leading oral and dental health problems encountered in our society; It can cause anxiety and pain, especially in children. A mistake that can be made during the correct emergency intervention and appropriate referral can bring along psycho-social problems as well as aesthetic problems. In this sense, dental traumas become one of the serious oral and dental health problems of childhood (29).

Many researchers from different countries have conducted surveys to measure the knowledge levels of various occupational groups about dentoalveolar injuries. Dentists, medical practitioners and dental hygienists are the leading profession groups. Considering the age group encountered, there are studies in which primary school teachers were also included due to these injuries also encountered in schools (30,31).

There are a limited number of studies in the literature that measure the knowledge and awareness levels of medical

and dental faculty students about dentoalveolar injuries (32). Within the scope of this survey study, it was aimed to determine the awareness of Dicle University Faculty of Medicine and Dentistry students about avulsion, one of the types of dental trauma, and to evaluate their knowledge level regarding treatment protocols.

While 34% of the medical faculty students and 86.67% of the dentistry students who participated in our study had not taken a trauma/emergency or first aid course before; 66% of the medical school and 13.33% of the dentistry faculty have previously taken a trauma/emergency or first aid course. Similar research conducted in Nepal; 36% of the students reported that they received training about traumatic injuries (33). Looking at these rates, it can be thought that there are deficiencies in the first aid course and it should be included in the curriculum more.

To the question in which their dental trauma experiences were investigated, 31% of our participants stated that they have not encountered tooth injury before. In a similar study conducted in Malaysia in 2020, 89.4% of the students; In another similar publication conducted in Spain in the same year, it was reported that 79% of the students did not see any dental injuries (32, 34). It can be concluded that the history of trauma occurs at different rates regardless of the regions.

Ideal treatment approach for permanent teeth with avulsion is to ensure the replantation of the relevant tooth at the accident site as soon as possible as International Association of Dental Traumatology (IADT)] (35). In this study, 23.46% of 4th grade participants and 12.32% of 5th Grade participants think that the appropriate time to get professional help is immediately. These data are obtained from De Souza Junior et al. As stated in the survey study they conducted on dentistry students in 2020, it corresponds with the students' insufficient level of knowledge about the negative impact of extra alveolar time (36). In Saudi Arabia, 67.5% of dentistry students answered the question about the ideal replantation time of the tooth correctly (37). This ratio is promising compared to other studies.

In cases where replantation is not possible as soon as possible, avulsed teeth should be stored in a liquid with an appropriate pH and osmolarity that can preserve the viability of periodontal ligament cells (16). In this study, while 28.67% of the participants stated that it can be preserved in milk, which is one of the suitable environments, no statistically significant relationship was found between the class variable and the environments where the removed tooth will be kept ($p>0.05$). In similar studies, the rates differed according to the classes. In a similar study conducted in Brazil, it was concluded that 50% of third grade students and 25% (average 62%) of fourth grade students would use milk as a storage medium until replantation (35). Another study conducted with Dentistry students in Santa Catarina showed that 28.8% of first-year students and 95.45% (average 62%) of graduating students would use milk as a storage medium (38). It was found that the values among dentistry students in Saudi Arabia were higher, and 77% of the students chose milk as the transport medium for an avulsed tooth (37). In a similar study conducted in Japan, it was observed that the values were lower. 26.4% of the third grade and 57.4% of the sixth grade of dental students chose fresh milk as the ideal medium for transplantation (39). Based on these data, it can be concluded that the answers given about suitable transport solutions are insufficient.

The question of how to clean an avulsed tooth if it is dirty, 56.33% of our participants stated that it will be cleaned by keeping it under tap water for a few seconds without rubbing. According to the 2020 IADT guidelines, this wash is gentle under saline solution or cold running water (32). In a similar study conducted in İstanbul in 2015, it was concluded that 79.3% of the students had sufficient knowledge on this subject (40).

There is a statistically significant relationship between the question "Can you replace a dislocated tooth?" and the class variable ($p<0.05$). 53.09% of the 4th grade students and 36.96% of the 5th grade students stated that they can replace the displaced tooth. It has been reported that 75% of the 4th grade students and 68.9% of the 5th grade students who participated in a similar survey in Malaysia gave a positive answer to this question (32). These rates are in parallel with our study.

‘’When the primary tooth comes out, can you replace it?” While 11.7% of our participants answered yes to our question, 88.3% answered no. In another study conducted in 2014, this question was answered as no at a rate of 86% (33). The guidelines of the American Academy of Pediatric Dentistry (AAPD) and the International Society of Dental Traumatology (IADT) do not recommend replantation of primary teeth due to the possibility of permanent damage to the permanent tooth germ (41).

The data obtained in our survey study showed that the students did not have sufficient first aid knowledge about dental avulsion and emergency response approaches. In similar studies, it was reported that the information about dental injuries of students was quite insufficient (42,43). In another published study, it was reported that only 8.1% of medical faculty students had sufficient knowledge of emergency response to avulsed teeth (44). In a similar study conducted in İzmir, it was concluded that the last year medical faculty students had insufficient knowledge about dental trauma (45).

CONCLUSION

Oral and dental health is an indispensable element for the individual's social status as well as individual well-being. During childhood, which is a very important period, it is critical to prevent possible dental traumas that may result in aesthetic loss or to overcome the table with the least damage possible with urgent and appropriate intervention in cases encountered.

This survey and literature reviews conducted clearly show that more comprehensive information about oral and dental health should be given in the undergraduate curriculum of the medical schools. Considering the data obtained in this study, it is thought that the medical and dental faculty students who came to the clinical stage of their education had insufficient knowledge about dental trauma, so it would be appropriate to provide oral and dental health information in a more comprehensive and understandable way in the education curriculum of the faculties. In this training, it will be appropriate to give interdisciplinary seminars, case presentations and lectures on practical emergency response on dental traum.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dicle University Faculty of Dentistry Ethics Committee (Date: 27.11.2019, Decision No: 2019/48)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Comparison of prognostic factors in patients diagnosed with endometrial cancer before and after COVID 19 pandemic: a retrospective study

Ahmet Bilgi[1], Fazıl Avcı[1], Havva Hande Keser Şahin[2], Bayram Can[1], Abdül Hamid Güler[1], Mehmet Kulhan[1], Çetin Çelik[1]

[1]Selçuk University Faculty of Medicine, Department of Gynaecology and Obstetrics, Konya, Turkey
[2]Hitit University Faculty of Medicine, Department of Pathology, Çorum, Turkey

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ABSTRACT

Aim: We aimed to compare prognostic factors in patients diagnosed with endometrial cancer before and after COVID 19 (Coronavirus Disease 19) pandemic.

Material and Method: This study was conducted in the Department of Gynecologic Oncology at Selçuk University Faculty of Medicine. After the World Health Organization (WHO) announced the COVID 19 pandemic on March 11, 2020, the Ministry of Health of the Republic of Turkey made an urgent decision on health services. The surgical cases diagnosed with endometrial cancer were divided into two groups based on the date when the pandemic was announced on March 11, 2020 and described group 1: 19 months before the pandemic, group 2: 19 months after the pandemic. Demographics, prognostic variables (stage, histologic type, grade, myometrial invasion, lymphovascular invasion, stromal involvement, and tumor size), endometrial cancer histological types, and treatment phases were all statistically assessed (early stage, advanced stage).

Results: A total of 194 cases were included, 96 cases in the first group and 98 cases in the second group. The mean age of the first group was 60.9±9.8 (40-86) years, the second group was 60.9±9.4 (36-82) years. There was statistically significant difference in clinicopathologic of endometrial cancer between group 1 and group 2, histologic type and grade (p=0.02; p=0.009 and p=0.018, respectively). There was no statistical difference between the two groups in age, stage, lymphatic and vascular space infiltration, muscular layer infiltration, interstitial infiltration and tumor size.

Conclusion: In the post-COVID 19 pandemic, more detection of type 2 of endometrial cancer, poor histological type and high grade, which have bad prognostic factors are found to be which may be due to the early admission of extra genital complaints. More randomized multicenter studies are needed on this subject.

Keywords: COVID 19 pandemic, endometrial cancer, prognostic factors

INTRODUCTION

As of the end of December 2019, the COVID 19 (Coronavirus Disease 19) infection has affected the World. During the pandemic, people's mental state has been affected by anxiety and depression (1). This situation has caused public health problems in Turkey and worldwide (2, 3). During the pandemic, the hospitalization rate, the number of patients requiring intensive care, and the COVID 19 infection rate have continued to increase (4, 5). Most hospital beds in most countries are crowded with COVID 19 patients. All specialist doctors are assigned to help COVID 19 patients, and elective surgeries were limited. Under these circumstances, the management of cancer patients has remained controversial. According to reports, cancer patients were found more susceptible to COVID 19 (6). However, during the COVID 19 epidemic numerous organizations such as the Gynecological Oncology Society (SGO), the European Gynecological Oncology Society (ESGO), and the Turkish Gynecological Oncology Society (TRSGO) gave their advice on how to treat patients with gynecological cancer (7, 8). In the study, titled "Cancer patients with SARS-CoV-2 infection: A nationwide analysis in China," patients diagnosed with cancer had a higher risk of being infected with COVID 19 than those without cancer, and cancer patients diagnosed with COVID 19 had worsening clinical outcomes (9). While surgical treatment for gynecological cancer is

Corresponding Author: Ahmet Bilgi, abilgi77@gmail.com
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curable, it has been shown that postponing treatment can result in poor outcomes (10).

Endometrial cancer is the most common type of gynecological cancer in developing countries. It is the second most common type of cancer after cervical cancer in the female population.(11). The average age of women diagnosed with endometrial cancer is 63, and more than 90% of endometrial cancer is diagnosed after the age of 50 (12). More aggressive histology and high grade malignancies have been documented in older women with poor prognosis associated with increased age (13, 14). In high-risk patients, treatment for endometrial cancer includes hysterectomy, bilateral salpingoooforectomy, and lymphadenectomy (12). While type 1 endometrial cancer accounts for around 80% of endometrial cancer, type 2 endometrial cancer accounts for the remaining 20% (15).

In this study, we aimed to compare of prognostic factors in patients diagnosed with endometrial cancer before and after COVID 19 pandemic periods.

MATERIAL AND METHOD

This study was approved by Selçuk University Local Ethics Committee (Date: 26.10.2021, Decision No: 2021/478). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted by the gynecological oncology department at Selcuk University, Faculty of Medicine. The Ministry of Health of the Republic of Turkey took immediate decisions for health services after the World Health Organization (WHO) declared the COVID 19 illness as a pandemic impacting the entire World on March 11, 2020. According to the date of the pandemic declaration in March 2020, the cases operated for endometrial cancer were separated into two groups: 19 months before the COVID 19 pandemic and 19 months after the COVID 19 pandemic. The study comprised 194 patients, with group 1 (n=96) before the COVID 19 pandemic and group 2 (n=98) after the COVID 19 pandemic. The FIGO (The International Federation of Gynecology and Obstetrics) 2009 staging and grading standards were used to stage all of the patients (16). Demographic factors, prognostic markers (stage, histomorphological type, grade, myometrial invasion, lymphovascular invasion, stromal involvement, and tumor size), endometrial cancer types (type 1 and type 2), and surgical types (early stage, advanced stage) were all analyzed statistically.

Statistical Analysis

Statistical evaluation was performed using the SPSS 20 (Statistical Package for Social Sciences) for Windows (IBM SPSS Inc., Chicago, IL) program. For homogeneity, the Kolmogorov-Smirnov test was applied. The categorical variables between groups were tested using the Chi-square test and Fisher's Exact test. Parametric variables were tested using the Student T test and the Mann-Whitney test, which is a non-parametric test. The p value of less than 0.05 was considered significant.

RESULTS

Group 1 had a mean age of 60.9±9.8 (40-86) while group 2 had a mean age of 60.9±9.4 (36-82) and mean age differences between the groups were not statistically significant. In terms of endometrial cancer clinicopathologic type, histomorphological type, and grade, there was a statistically significant difference between groups 1 and 2 (p=0.02, p=0.009, and p=0.018 respectively). Group 2 had a higher rate of type 2 endometrial cancer and grade 3 than group 1. There was no significant difference between the grade 1 and 2 groups. In terms of stage, type of stage, lymphovascular space invasion, myometrial invasion, stromal invasion, and tumor size, there was no statistically significant difference between the two groups. Data of patients diagnosed with endometrial cancer were presented in **Table 1**.

Table. Datas of patients diagnosed with endometrial cancer

	Before COVID 19 n=96	%	After COVID 19 n=98	%	P
Age (year)	60.9±9.8 (40-86)		60.9±9.4 (36-82)		0.640
Clinicopathologic types					0.02
Type 1	82	85.4	71	72.4	
Type 2	14	14.6	27	27.5	
Histology					0.02
Endometrioid	90	88.7	76	77.5	
Serous	6	11.3	16	16.3	
Mucinous	0	0	3	3.06	
Clear cell	0	0	2	2.04	
Neuroendocrine	0	0	1	1.02	
Grade					0.083
1	55	57.3	46	46.9	0.097
2	27	28.1	25	25.5	0.402
3	14	14.6	27	27.5	0.02
Stage					0.487
Stage 1	73	76.0	74	75.5	0.220
Stage 2	0	0	4	4.1	
Stage 3	17	17.7	16	16.3	
Stage 4	6	6.2	4	4.1	
Stage type					0.336
Early	73	76.04	78	79.6	
Advanced	23	23.9	20	20.4	
LVSI					0.398
Yes	17	17.3	15	15.3	
No	79	82.2	83	84.7	
Myometrial invasion					0.281
Yes	26		22	22.4	
No	70	72.9	76	77.5	
Stromal invasion					0.176
Yes	12	12.5	18	18.4	
No	84	87.5	80	81.6	
Tumor size (cm)	4.3±2.1 (3.9-4.77)		4.6±2.6 (4.0-5.1)		0.304

DISCUSSION

In today's COVID 19 pandemic, the care and safety of cancer cases is critical, and most cancer centers must develop an emergency plan because of the immunosuppressive state created by both anticancer medications and surgery, cancer patients are more susceptible to infections (17-19). At the same time, the COVID 19 pandemic has had a negative impact on people's mental health. Clinicians should be aware of posttraumatic stress disorder (PTSD), weakness, exhaustion, and anxiety (1). As a result, most cancer patients might be unconcerned about their complaints, paid little attention to them, and either did not go to the doctor or went late, resulting in the disease progressing to an advanced stage.

The endometrioid type of endometrial cancer is the most prevalent histological type. The endometrioid type of endometrial cancer that has good prognosis, causes abnormal uterine bleeding in the early stage. As a result, when patients arrive at the clinic, up to 70% of cases are diagnosed at stage 1 (20). Types of endometrial cancer include those that are estrogen-dependent (type 1) and those that are estrogen-independent (type 2) (21). Serous and clear cell tumors, which are histological forms of endometrial cancer with poor prognosis, have a higher incidence of myometrial invasion, vascular invasion, and peritoneal carcinomatosis (22). Endometrial tumors that are not estrogen-dependent have a low incidence but a high malignancy and a poor prognosis (23, 24). Besides, serous and clear cell histologic types have had high rates of extragenital spread and recurrence (25). Regardless of grade or stage, metastatic endometrial cancer has a bad prognosis, and the overall survival rate is dramatically reduced (26). There is a 5-year overall survival rate of 80-90 % in stage 1, 70-80% in stage 2, and 20-60% in stage 3-4 in the prognosis that correlates with the stage and grade of cancer (16).

In patients who came to our clinic before and after COVID 19 pandemic, there was no statistically significant difference between the two groups in terms of age, stage, type of stage (early stage and advanced stage), lymphovascular space invasion, myometrial invasion, stromal invasion, and tumor size. However, between the two groups, there was an increased frequency of type 2 endometrial cancer, poor histological types (serous, clear cell, neuroendocrine), and a high grade (grade 3), which is an indicator of poor prognosis.

Alemderoglu et al. (27) showed a significant difference between two groups (>70 age and 70 age) in terms of non-endometrioid histology, high-grade malignancies, and >50 myometrial invasions. However, FIGO stages of both groups were similar. Type 1 endometrial cancer was observed at a rate of 78.9% in our study, while type 2 endometrial cancer was observed at a rate of 21.1% in this study. This rate is smilar to with previous research. However, type 2 endometrial cancer was found at a statistically significant rate of 14.6 percent in group 1 and 27.5 percent in group 2 (p=0,02) As a difference from Alemderoglu study, this study consist on similar age group and COVID 19 pandemic. Besides, there is no study about this topic.

Dolyy et al. (27) showed that a protracted delay between diagnosis and treatment period resulted in an important decrease in survival in a single-center 7-year retrospective study of 889 endometrial cancer diagnoses. Cortilla et al. (10) reported that focusing health resources on COVID 19 and delaying normal oncological treatments during the pandemic period can result in poor outcomes in cancer cases. Furthermore, it has been stressed that postponing surgical operations will cause progression of cancer and be inoperable of malignancy from being curable.

The limitation of this study is that the status of COVID 19 cases is not known retrospectively and the study is in a single center. In this study, while we expect the cases to be in advanced stages due to be delayed and be neglected of complaint of abnormal uterine bleeding, which is the most common complaint in endometrial cancer, due to stress of COVID 19 in women, the situation we encounter in the clinic is at the same stage in the pre-COVID 19 and post-COVID 19 periods, but factors such as type 2 endometrial cancer, poor histologic types (serious, clear cell and neuroendocrine), and high grade (grade 3) are all frequently found in the post-COVID 19 period, which is surprising. We think that this may be due to the early admission of patients with poor prognostic types to the clinic.

CONCLUSION

As a result, while endometrial cancer is the most common cancer in developed countries, the most common reason for admission is abnormal uterine bleeding. During COVID 19, gynecological surgery can be performed under suitable conditions. Early detection of endometrial prognostic factors will improve the early diagnosis of endometial cancer and increase the survival rate of cases. In the post-COVID 19 period in endometrial cancer, more detection of type 2 endometrial cancer, poor histologic types, and high grade (grade 3) may be due to early admission because of extra genital complaints. The early detection of endometrial cancer in the two groups and the fact that the stages of the two groups are the same support this study. More randomised control trials are needed on this topic.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Selçuk University Local Ethics Committee (Date: 26.10.2021, Decision No: 2021/478).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Hyperlipidemia in post-COVID patients; a unique observational follow-up study on lipid levels in post-COVID patients

Oğuz Abdullah Uyaroğlu, Murat Özdede, Nursel Çalık Başaran, Bahadır Köylü, Taha Koray Şahin, Lale Özışık, Mine Durusu Tanrıöver, Gülay Sain Güven

Hacettepe University, Faculty of Medicine, Department of Internal Medicine, Section of General Internal Medicine, Ankara, Turkey

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ABSTRACT

Aim: Alterations in plasma lipid levels have been shown to be correlated with the severity of infections due to various pathogens such as bacteria, viruses. In this study, we aimed to evaluate the lipid metabolism changes associated with disease severity and prognosis in hospitalized COVID-19 patients during and after (post-COVID) the disease.

Material and Method: Patients who were hospitalized in the COVID-19 wards between April 02, 2020, and November 20, 2020 and were then evaluated in the follow-up outpatient clinic were retrospectively searched.

Results: Lipid levels were present at the admission and follow-up for 95 patients. The mean (S.D) age was 48.49 (16.4), and 49(51.6%) were male. The mean (S.D) day between the admission and the first visit in the COVID-19 follow-up outpatient clinic was 27.8 (12.8). LDL-C (p=0.044), and HDL-C (p=0.004) levels were significantly lower in the severely ill group at the admission. Total cholesterol, LDL-C, HDL-C, and triglyceride levels on follow-up were significantly higher than those levels on the admission day (p<0.001). Delta (Follow up-Admission) levels LDL-C, total cholesterol and triglyceride levels were significantly high in patients who have received steroid therapy. Only delta LDL-C was significantly high in patients who require Intensive Care Unit.

Conclusions: Dyslipidemia is observed in COVID-19 patients both during the disease and in the post-COVID period. Our findings also support the evidence demonstrating that low LDL-C and/or HDL-C levels can increase the risk of developing severe infections, also in COVID-19. The dynamics of lipid profiles before/during and after the entire disease course should be monitorized.

Keywords: COVID-19, dyslipidemia, hyperlipidemia, post-COVID, long-COVID

INTRODUCTION

Although almost two years have been since the start of the Coronavirus Disease 2019 (COVID-19) pandemic, data on the pathophysiology, predictors of severity, and treatment of the disease are still incomplete. To date, thousands of reports have emerged on almost every aspect of COVID-19 and the literature is still growing with new pieces of evidence. However, we still have limited information regarding lipoproteins and COVID-19.

Acute infections have been shown to lead to significant alterations in metabolic regulation, including lipids and lipoproteins, which play a central role in the host immune response (1). The common lipid alterations include a decrease in total cholesterol (TC) and an increase in the concentration of triglyceride (TG) -rich lipoproteins. Additionally, low- and high-density lipoprotein - cholesterol (LDL-C and HDL-C, respectively), apolipoprotein-A1, and apolipoprotein-B levels decrease (1-3). The role of lipid levels as a marker of infection severity and prognosis has been investigated and HDL-C, apo-A1 and LDL-C have been shown as prognostic markers in patients with sepsis, pneumonia and other infections (4,5).

Alterations in lipid and lipoproteins in COVID-19 patients have been observed and dyslipidemia has been associated with the inflammatory response, disease severity and poor prognosis. LDL-C, TC and HDL-C concentrations significantly decreased in COVID-19 patients (6-10). Although most of the studies were in

Corresponding Author: Oğuz Abdullah Uyaroğlu, oguzuyaroglu@hotmail.com
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hospitalized patients, literature on lipid profiles during follow-up in discharged COVID-19 (post-COVID) patients is rare (11-12).

In this real life, observational follow-up study, we aimed to evaluate the association of lipid metabolism changes with disease severity and prognosis in hospitalized COVID-19 patients during and after the disease.

MATERIAL AND METHOD

The study was carried out with the permission of Hacettepe University Non-Interventional Clinical Researchs Ethics Committee (Date: 31.03.2020, Decision No: 20/353). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

This study was conducted in an accredited tertiary care hospital. A "COVID-19 follow-up outpatient clinic" was established in the initial stages of the pandemic to address and manage the clinical needs of non-critical COVID-19 adult patients after discharge (post-COVID). Patients who were hospitalized in the COVID-19 wards were scheduled a follow-up visit in the 2-4 weeks at the time of discharge.

Patients who were hospitalized in the COVID-19 wards between April 02, 2020, and November 20, 2020 and were then evaluated in the follow-up outpatient clinic were retrospectively searched from a prospectively formed database. Patients who had polymerase chain reaction (PCR) confirmed COVID-19 were screened. Those who had plasma lipid levels measured at the time of admission in the COVID-19 wards and in the COVID-19 follow-up outpatient clinic thereafter were included. As this was a retrospective study, there was no intervention to the management of the patients. Patients on statin treatment continued to take their drug while those who were not on statins were not initiated statin treatment during the study period.

The clinical severity of the patients was graded as mild, moderate or severe according to the World Health Organization (WHO) classification (13). Patients who were graded as critical at the time of admission and hospitalized directly to intensive care units (ICU) were not included.

Statistical Analysis

Statistical analysis was performed with IBM SPSS for Windows version 23 package. Normally distributed continuous data were summarized by mean±standard deviation (SD), while non-normally distributed continuous data were summarized by median [25-75th percentiles]. The Chi-square test or Fisher exact test were applied to detect the relation between categorical variables. Independent sample t-test or Mann Whitney U test was used to compare independent two groups in terms of numerical data. Within group differences were shown by Wilcoxon test. A 2-tailed p value of 0.05 was considered significant.

RESULTS

A total of 1105 adult patients with laboratory confirmed COVID-19 were hospitalized in COVID-19 wards. Plasma lipid levels of 108 patients were available at the time of admission, among whom 95 had been evaluated in the follow-up clinic and plasma lipid levels were available (**Figure 1**).

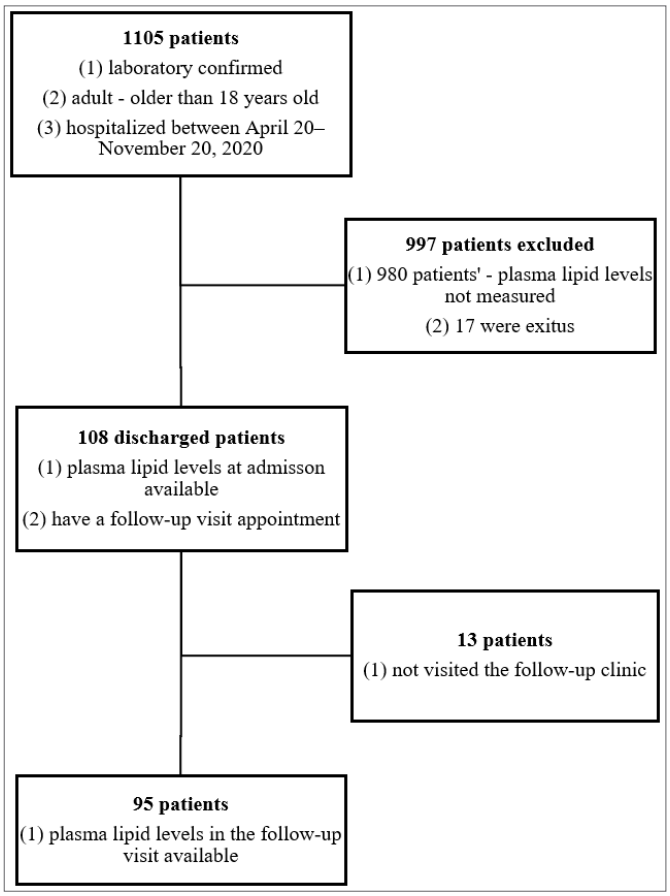

Figure 1. Flowchart of the patient selection

Baseline Characteristics and Plasm Lipid Values at the Time of Admission

The mean (SD) age of the patients was 48.5 (16.4) years, and 49 (51.6%) were male. The median length of stay (LoS) was 6 (IQR=5) days. Baseline characteristics of patients and plasma lipid levels at admission are given in **Table 1**.

The median time from symptom onset to hospital admission (on the day of venous sampling for lipid parameters) was 3 (IQR=4) days. The median (IQR) HDL-C, LDL-C, TC and TG levels were 38.1 (15.1), 106.8 (52), 168.2 (62.1) and 119.5 (89) mg/dL, respectively.

Table 1. Baseline characteristics of the patients and plasma lipid levels at the time of admission

	Total, n=95 (%)	HDL-C median (IQR), mg/dL	P	LDL-C median (IQR), mg/dL	P	Triglycerides median (IQR), mg/dL	P	Total cholesterol median (IQR), mg/dL	P
Age, years, mean (S.D.)	48.49 (16.4)								
Plasma lipid level, median (IQR)		38.1 (15.1)		106.8 (53)		119.5 (89)		168.2 (62.1)	
Sex, n (%)			<0.001		0.771		0.474		0.760
Female	46 (48.4)	45.2 (14.6)		112.85 (47.5)		126 (87)		167.8 (67.9)	
Male	49 (51.6)	34.2 (13.3)		98.9 (65.1)		114 (83)		168.6 (60)	
Smoking, n (%)			0.031		0.066		0.619		0.204
Never smokers	68 (71.6)	40.5 (16.8)		113.35 (51.9)		116 (87)		185.6 (64.3)	
Active smoker	15 (15.8)	34.5 (14.2)		91.7 (39.3)		112 (100)		149.3 (61.4)	
Ex-smoker	11 (11.6)	30.7 (14.0)		121.0 (56.0)		148.0 (65.0)		177.3 (66.7)	
Chronic diseases, n (%)									
Type 2 diabetes mellitus	29 (30.5)	34.95 (12.7)	0.011	111 (54.8)	0.599	151 (76)	0.001	184.6 (78.7)	0.357
Hypertension	35 (36.8)	37.0 (13.8)	0.108	111 (53)	0.666	137 (80)	0.026	166 (68.75)	0.693
Coronary artery disease	13 (13.7)	32.5 (11.8)	0.036	93.0 (34.0)	0.324	162 (77)	0.019	167.6 (54.18)	0.884
COPD	8 (8.4)	39.55 (17.8)	0.850	106.35 (65.3)	0.880	102.0 (79)	0.750	160 (92.73)	0.637
Medications, n (%)									
ACE/ARB	26 (27.4)	38.65 (14.2)	0.550	109 (48.4)	0.920	130.5 (58)	0.160	165.9 (66.9)	0.830
Metformin	18 (18.9)	34.5 (12.5)	0.018	103.95 (43.3)	0.595	148.0 (57)	0.029	169.2 (74.7)	0.800
Statin	8 (8.4)	27.3 (11.0)	0.006	89.5 (25.4)	0.142	158.0 (197)	0.198	147.6 (72.4)	0.232
Asetil salicylic acid	13 (13.4)	31 (22)	0.382	95.6 (38.5)	0.420	151 (92.0)	0.484	164.8 (61.9)	0.549
Beta-blocker	17 (17.9)	34.0 (14.0)	0.022	121.4 (66.5)	0.273	158 (113)	0.085	172.2 (83.35)	0.576
Calcium channel blockers	6 (6.3)	32.4 (10.1)	0.185	100.45 (78.7)	0.387	96.5 (153)	0.862	164.1 (108.3)	0.477
Disease severity, n (%)			0.004		0.044		0.161		0.091
Mild	55 (62.1)	40.0 (12.7)		106.6 (46.4)		112 (97)		161.7 (55.7)	
Moderate	26 (27.4)	38.65 (19.2)		130.3 (59.7)		128 (74)		203.2 (103.3)	
Severe	10 (10.5)	27.1 (5.9)		89.25 (39.8)		148 (86)		139.6 (57.7)	
Treatment, n (%)			0.351		0.110	85 (90)	0.352		0.062
No treatment	5 (5.3)	31.3 (13.4)		73.1 (60.1)				130.5 (62.1)	
Hydroxychloroquine	11 (11.6)	44.6 (7.9)		84.5 (62.5)		112 (73)		152.5 (69.5)	
Hydroxychloroquine + AZ	11 (11.6)	40.7 (15.1)		98.1 (39.0)		86 (52)		151.4 (51.6)	
Hydroxychloroquine + AZ + FAV	10 (10.5)	30.5 (22.5)		116.9 (66.3)		105 (61)		194.1 (81.5)	
Hydroxychloroquine + FAV	4 (4.2)	39.2 (33.8)		90.6 (41.1)		137 (112)		138.4 (78.7)	
Favipiravir (FAV)	54 (56.8)	38.1 (16.4)		113.3 (52.3)		74.5 (64)		186.5 (62.85)	
Corticosteroids add-on, n (%)	8 (8.4)	28.5 (28.8)	0.081	93 (77)	0.328	96 (100)	0.254	137.5 (89.2)	0.040
Intensive Care Unit requirement	10 (10.5)	29.2 (13.8)	0.010	93.6 (66.4)	0.524	126 (65)	0.746	155.2 (89.2)	0.389

S.D.; standard deviation, COPD; Chronic obstructive pulmonary disease, ACE/ARB; Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers, AZ; Azithromycin

Median HDL-C levels were significantly lower in males than females at admission (20.7 vs 45 mg/dL, respectively; p<0.001) and were higher in never smokers than remains (p=0.031). Among patients who had type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) median HDL-C levels were significantly lower than those who did not have T2DM (34.95 vs 41.25 mg/dL, p=0.011) and CAD.(32.55 vs 39.45 mg/dL, p=0.036). Median HDL-C levels were significantly lower in patients on metformin (34.5 vs 40.5 mg/dL, p=0.018) and beta-blocker (34.0 vs 40.5 mg/dL, p=0.022) therapy than those who did not take these medications.

Median TG levels were higher in patients with T2DM (151 vs 105 mg/dL, p=0.001), hypertension (HT) (139 vs 137 mg/dL, p=0.026) and CAD (162 vs 114 mg/dL, p=0.019) than those who did not have these diseases. In addition, also patients on metformin therapy had significantly higher median TG levels than those who did not use metformin (148 mg/dL vs 112 mg/dL, p=0.029).

There was no significant difference in median LDL-C and TC levels with regards to age, sex, smoking status, existing diseases and medications used.

Eight (8.4%) of the patients were on statin treatment and no new statin therapy was initiated in any patient during hospitalization. While there was no significant difference in median LDL-C, TG, and TC levels in patients on statin treatment, HDL-C (27.3 vs mg/dL vs 39.1, p=0.006) was significantly lower compared to non-users.

Severe patients had significantly lower HDL-C (28.7 mg/dL, p=0.004) and LDL-C (93 mg/dL, p=0.044) levels in comparison with mild and moderate patients. The patients who require ICU during hospitalization had also lower HDL-C (29.2 vs 39.9 mg/dL, p=0.010) than those who do not require ICU.

Plasma Lipid Values at the Time of Follow-up Visit

The mean (SD) time period between the admission and the first visit in the COVID-19 follow-up outpatient clinic was 27.8 (12.8) days.

The median (IQR) HDL-C, LDL-C, TC and TG levels were 45.5 (15.1), 125 (43.6), 207 (67.5) and 148 (153) mg/dL, respectively. Plasma HDL-C, LDL-C, TC and TG levels on follow-up were significantly higher than those on the admission (p<0.001) (**Figure 2**).

There was no significant difference in the increment in plasma lipid levels with regards to age, sex, existing diseases and medications used (**Table 2**). Delta (Follow up-Admission) TG (26.9 mg/dL, p= 0.030) and delta TC (25.5 mg/dL, p= 0.026) levels were significantly lower in never smokers than remains.

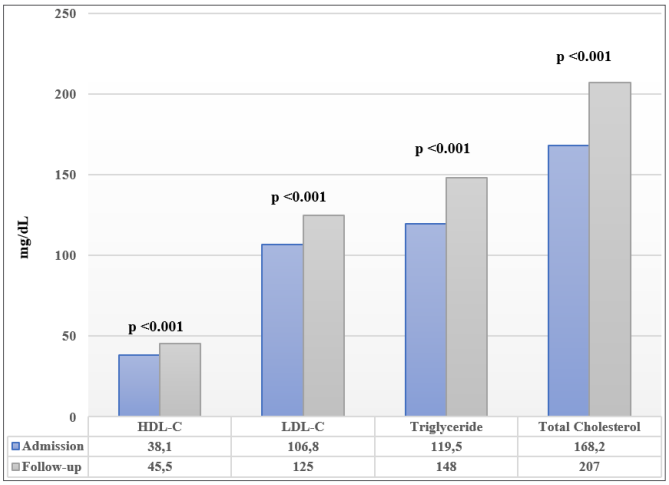

Figure 2. Plasma lipid levels of the study patients at the time of admission and in the follow-up visit

Table 2. Delta (the difference between the values in the follow up clinic and at the time admission) plasma lipid levels

	Total, n=95	Delta HDL-C median (IQR), mg/dL	P	Delta LDL-C median (IQR), mg/dL	P	Delta triglycerides median (IQR), mg/dL	P	Total cholesterol median (IQR), mg/dL	P
Age, years, mean (S.D.)	48.4 (16.4)								
Delta lipid levels, median (IQR)		5.9 (9.5)		16.3 (24.8)		59.3 (68.2)		35.1 (48.7)	
Sex, n (%)			0.821		0.540		0.203		0.24
Female	46 (48.4)	6.3 (11.5)		14.8 (26.5)		34.6 (100.2)		28.4 (40.2)	
Male	49 (51.6)	6.8 (7.5)		18 (23.2)		79.4 (213.2)		40.7 (54.6)	
Smoking, n (%)			0.690		0.372		0.030		0.026
Never smokers	68 (71.6)	6.1 (10.7)		14.1 (26.4)		26.9 (82.8)		25.5 (42)	
Active smokers	15 (15.8)	6.6 (5.4)		21.1 (16.1)		134.1 (343.1)		54.5 (67.2)	
Ex-smokers	11 (11.6)	8.8 (7.2)		23.4 (24)		132.1 (165.3)		58.7 (42.9)	
Chronic diseases, n (%)									
Type 2 diabetes mellitus	29 (30.5)	6.8 (6)	0.913	12.5 (24.9)	0.300	104.5 (288.3)	0.285	38.8 (64.1)	0.654
Hypertension	35 (36.8)	7.8 (6.6)	0.413	15.1 (23.5)	0.670	43.9 (116.9)	0.580	30.3 (38.1)	0.371
Coronary artery disease	13 (13.7)	12 (7.6)	0.685	14.9 (30.6)	0.840	53.9 (177.3)	0.915	3.1 (52.5)	0.873
COPD	8 (8.4)	6.6 (9.8)	0.889	0.2 (25)	0.098	193.7 (503.8)	0.029	42.5 (106.2)	0.682
Medications, n (%)									
ACE/ARB	26 (27.4)	7.2 (6.9)	0.698	14.9 (25.9)	0.708	61 (118.6)	0.942	34.1 (40.7)	0.899
Metformin	18 (18.9)	5.5 (5.6)	0.642	18.2 (12.5)	0.744	60.8 (115.2)	0.961	37.1 (40.1)	0.866
Statin	8 (8.4)	10.4 (5.4)	0.274	27.2 (33.2)	0.201	33 (164.3)	0.687	45.5 (59.9)	0.562
Asetil salicylic acid	13 (13.4)	8.7 (7.7)	0.443	22.9 (28.5)	0.350	59 (133.5)	0.998	45.2 (53.7)	0.490
Beta-blocker	17 (17.9)	7.3 (5.6)	0.784	15.1 (28.5)	0.802	98.2 (172)	0.373	41.8 (54.1)	0.580
Calcium channel blockers	6 (6.3)	7.8 (3.1)	0.470	20.3 (17.8)	0.696	159.8 (210.6)	0.136	60.1 (45.5)	0.195
Disease severity, n (%)			0.045		0.100		0.196		0.112
Mild	55 (62.1)	5.8 (8.8)		14.4 (21.7)		37.3 (47)		27.9 (37.3)	
Moderate	26 (27.4)	6.2 (11.7)		12.6 (31.4)		113.6 (282.5)		41.6 (68.9)	
Severe	10 (10.5)	14.1 (13.6)		37.5 (23.8)		52.5 (159.5)		62.2 (40.7)	
Treatment, n (%)			0.077		0.117		1.710		0.072
No treatment		14.7 (20.6)		26.6 (35.3)		78.2 (190.3)		128.8 (33.8)	
Hydroxychloroquine		2.4 (3.9)		2.50 (18.0)		24.7 (36.2)		169.7 (39.1)	
Hydroxychloroquine + AZ		5.9 (3.9)		15 (21)		28.5 (28.5)		162.1 (36.4)	
Hydroxychloroquine + AZ + FAV		12.3 (9.1)		28.3 (27)		202.7 (439.2)		190.9 (46.1)	
Hydroxychloroquine + FAV		11.5 (7.3)		33.8 (10.9)		14.7 (36.8)		154.7 (45)	
Favipiravir (FAV)		5.5 (9.7)		15.2 (24.9)		50.1 (115.5)		189 (50.2)	
Corticosteroids add-on, n (%)	8 (8.4)	6.2 (8.1)	0.912*	42.4 (16.9)	0.004*	173.4 (127)	0.042*	83.3 (37.2)	0.004*
Intensive Care Unit requirement	10 (10.5)	12.1 (14.2)	0.242*	29.6 (26.1)	0.045*	191 (435.7)	0.341*	79.9 (78.9)	0.096*

S.D.; standard deviation, COPD; Chronic obstructive pulmonary disease, ACE/ARB; Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers, AZ; Azithromycin, * T-test

There was no statistically significant increase in lipid profiles in terms of disease severity, except HDL-C. HDL-C increased more in the severely ill patient group (delta HDL-C; 14.1, p=0.045) which was lower on the admission in comparison with mild and moderate patients.

Antiviral treatment protocols for SARS-CoV-2 infection had no effects on the incremental values. Delta LDL-C (42.4 mg/dL, p=0.004), TG (173.4 mg/dL, p=0.042), and TC (83.3 mg/dL, p=0.004) levels were significantly higher in patients who have received corticosteroid therapy. Only delta LDL-C (29.6 mg/dL, p=0.045) was significantly higher in patients who require ICU during hospitalization.

Since the trend of increase in lipid levels was observed especially in patients with low lipid levels on admission, subgroups were created as above and below average lipids in the cohort, and lipid increment was re-examined according to the subgroups. In the patient group presenting with low LDL-C (<100 mg/dL) on admission, the increase in LDL was significantly higher than the rest of the cohort (Delta LDL (mean/SD); 25.5/22.3 mg/dL, p=0.001). In patients with low TG (<150 mg/dL), a similar pattern is observed only in TG levels, but it is not statistically significant (Delta Triglyceride (mean/SD); 91.14/222.151 mg/dL, p=0.075). Individuals presenting with low HDL-C (<40 mg/dL) showed an increase in all parameters during the post-COVID and it was statistically significant (Delta HDL-C (mean/S.D); 9.87/8.401 mg/dL, p=<0.001), (Delta LDL-C (mean/S.D); 25.49/21.06 mg/d, p=<0.001), (Delta TG (mean/S.D); 86.83/218.27 mg/dL, p=0.069), Delta TC (mean/S.D); 53.29/49.95 mg/dL, p=<0.001).

DISCUSSION

In this real-life study, we evaluated the lipid metabolism changes in 95 hospitalized COVID-19 patients during and after the disease and the association of lipid levels with disease severity and prognosis. Alterations in lipid levels have been seen both at admission (in acute phase) and after discharge (post-COVID). While lipid levels were generally lower at admission in patients with some existing diseases (T2DM, HT, CAD), taking drugs (metformin, beta-blockers, statins) and the severity of the disease, all lipid levels were found to increase significantly after COVID.

Lipids have a valuable function in the pathophysiology of viral pneumonia. Native surfactant lipids have been recognized recently as key regulators of lung inflammation that occupy a common ground at the intersection of tissue homeostasis, host defense, and biophysics (14). It has recently been shown that diet-induced dyslipidemia alters trafficking of immune cells to the lung in a manner that may have important implications for the pathogenesis of acute lung injury, asthma, pneumonia, and other lung disorders (15). Acute inflammation caused by viruses may result in dyslipidemia in patients, and lipid metabolism is known to play an important role in the host immune response. Studies showed alterations in lipid levels in acute Epstein-Barr virus (EBV) infection (lower concentrations of apoA-I, HDL-C, TC, LDL-C), cytomegalovirus (CMV) infection (lower HDL-C) and in dengue-positive patients (lower HDL-C and LDL-C) (16-18). Remarkably, while SARS patients had lower concentrations of apoA-I in the acute phase, altered lipid metabolism has been shown in recovered SARS-CoV-1 patients even 12 years after the infection (19-20).

Detailed information on the changes in lipid profiles during COVID-19 infection is lacking. Wang et al. (21) showed that loading cells with cholesterol from blood serum using the cholesterol transport protein apolipoprotein E (apoE) enhances the entry of pseudotyped SARS-CoV-2 and the infectivity of the virion. Wang et al. (21) suggest that cholesterol concomitantly traffics ACE2 to viral entry sites, where SARS-CoV-2 docks in order to properly exploit entry into cells. Therefore, decreased cholesterol levels in the blood may indicate severe loading of cholesterol in peripheral tissue and escalated SARS-CoV-2 infectivity. In a recent study, abnormal lipid metabolism has been demonstrated in cured COVID-19 patients when they were about to be discharged from the hospital, indicating that viral infection and drug treatment affected the patients' systemic metabolism (11). In the related study a high-resolution mass spectrometry-based lipidomic strategy was used to characterize the endogenous plasma lipids and most of the significantly changed lipids were up-regulated in cured patients. A positive correlation existed between the alteration of lipids and deterioration of the disease (11). In addition, several different hypotheses related to dyslipidemia in COVID-19 have been stated such as reduction of LDL-C biosynthesis with damage of liver function caused by SARS-CoV-2, dyslipidemia due to acute inflammation (inflammatory cytokines, such as TNF-alfa, IL-6, and IL-1 beta, have been shown to modify lipid composition), increased vascular permeability, degradation of lipids due to generally elevated free radical signals in infected host cells, leakage of LDL-C into alveolar spaces to form exudates and suppress the levels of many proteins related to cholesterol metabolism (22,23).

Recent studies have reported that hypolipidemia in hospitalized COVID-19 patients at the admission and the decrease in lipid levels were associated with the severity of the symptoms (6-10,12,14,15). In one of the first studies

early in the pandemic, patients with COVID-19 develop hypolipidemia as early as when they have mild symptoms and a reduction of lipid levels in patients with COVID-19 has an association with the severity of the symptoms (23).

In our study, median HDL-C was 38.1 (15.1) mg/dL and lower in males, and lower HDL-C was correlated with the severity of COVID-19 consistent with the literature. Severe patients and the patients who required intensive care during hospitalization had lower HDL-C at the time of admission. In a study from China, HDL-C was negatively correlated with c-reactive protein (CRP) and positively correlated with lymphocytes and found and independent association with the severity of COVID-19 as a predictor (8). In another study, low concentrations of HDL-C and apoA-I at admission were significantly associated with high concentrations of CRP, prolonged hospital stay and increased disease severity (6). In an observational study, low HDL-C in COVID-19 patients was correlated with a higher risk of developing severe events (9). In a cross-sectional study including 1411 hospitalized patients with COVID-19 and an available standard lipid profile prior (n:1305) or during hospitalization (n:297), patients with severe COVID-19 progression had lower HDL-C and higher TG levels before the infection (10). Median HDL-C levels were also significantly lower in patients with T2DM and CAD, which are poor prognostic factors for COVID-19 (24). On the other hand, while HDL-C and LDL-C levels upon ICU admission were low in severe COVID-19 patients, they were not found to be associated with poor outcomes (9).

In the present study, severe patients had also lower LDL-C at the admission. Lower serum levels of LDL-C and TC at admission were found as an independent predictor of LoS prolongation (2). In a small cohort of 21 patients, lipid profiles were checked before viral infections and during the course of their illness, and demonstrated that the degree of decreased LDL-C was associated with severity and mortality of the disease (25).

The most distinctive feature of this study is the follow-up lipid levels of the patients after discharge (post-COVID). All plasma lipid levels (HDL-C, LDL-C, TG and TC) on follow-up were significantly higher than those levels on the admission. The change in the pattern of increase in lipid levels was most evident in the severity of disease (HDL-C), corticosteroid use (LDL-C, TC, TG), and the need for ICU (LDL-C). Previous studies have demonstrated an increase in lipid levels during the course of the disease (in recovery phase and/or during hospitalization). In a study from China, in 68 severe cases, serum lipids were followed up three times with 5-10 days intervals during hospitalization. The median LoS was 29 days. The average levels of HDL-C, LDL-C, TG and TC, in 68 severe cases gradually and significantly increased during the following in the 2nd (except for LDL-C) and 3rd tests (both $p < 0.05$) (2). In another study, lipid profiles were analyzed on admission (day 1), on days 5–7 and days 15–17 after admission. From day 1 to day 15–17, TC, LDL-C, HDL-C and apoAI showed a slow upward trend in survivors, but maintained lower concentrations or showed a rapid downward trend in non-survivors (6). In a follow up study from China, LDL-C, HDL-C and TC were all significantly higher at follow-up than at the time of admission in severe/critical cases. LDL-C and TC levels were significantly higher at follow-up than at the time of admission in mild patients. The overall follow-up time was 100 days after discharge (12). In our study, HDL-C increased more in the severe patient group, although lower at presentation, confirming that HDL-C is a prognostic marker.

In our study delta (Follow up-Admission) LDL-C, TG and TC levels were significantly higher in patients who have received corticosteroid therapy. All patients were given 6 mg/day p.o dexamethasone totally for 10 days in accordance with the local guidelines (13). Although all of the patients receiving corticosteroids were in the severely ill group, it was remarkable that only LDL-C, TG and TC increased significantly. The increase in HDL-C, which is significant in severe patients, was not significant in patients receiving corticosteroids. This situation may also support that HDL-C may be a predictor associated with the pathogenesis of COVID-19.

The clinical meaning and consequences of low lipid levels on admission (during the disease period) and the increase in the recovery period (post-COVID) are unknown. It is not known whether the surge in lipid levels consists only of a reactive process or that it may be associated with endothelial damage and vascular events during the recovery period. Whether this is a reactive increase or the effect of reverting to the patient's basal lipid profiles is unknown.

Our study has some limitations. This is a single centered study. Although the results are consistent with the literature, the sample size is small. Although the lipid levels of the patients seemed to be low at admission, it would have been better to know the basal lipid levels before the disease.

CONCLUSION

This study is valuable in that it confirms the dyslipidemia seen in previous studies in COVID-19 patients, as well as being one of the first studies in the literature in terms of showing the course of dyslipidemia in the post-COVID period. Dynamics of lipid levels before, during and after the entire disease course in a large cohort of COVID-19 patients should be monitored for better characterization of dyslipidemia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hacettepe University Non-Interventional Clinical Researchs Ethics Committee (Date: 31.03.2020, Decision No: 20/353).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: A part of this study has presented as e-poster on 89th European Atherosclerosis Society (EAS) Congress in May 30 – June 2, 2021 (Abstract 1066 - Title: Can Plasma Lipid Levels Be Correlated To Severe COVID-19 Infection?)

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Medical device related pressure injuries in COVID-19 patients followed up in an intensive care unit

Tuna Ertürk[1], Demet İnangil[2], Elif Lale Pakdil[1], Nilüfer Ertürk[1], İlayda Türkoğlu[2], Merdiye Şendir[2], Berna Dinçer[3], Hatice Erdoğan[4], Füsun Afşar[1], Ayşın Ersoy[1]

[1]University of Health Sciences, Sultan 2. Abdulhamid Han Training And Research Hospital, Department of Anesthesiology, İstanbul, Turkey
[2]University of Health Sciences, Hamidiye Faculty of Nursing, İstanbul, Turkey
[3]İstanbul Medeniyet University, Faculty of Health Sciences, Department of Nursing, İstanbul, Turkey
[4]İstanbul Maltepe University, School of Nursing, İstanbul, Turkey

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ABSTRACT

Aim: The aim of this study is to determine the prevalence of medical device-related pressure injuries in COVID-19 patients.

Material and Method: This study was conducted with a cross-sectional and retrospective design. The data of 436 patients who were followed up and treated in the Anesthesia and Reanimation Intensive Care Unit with the diagnosis of COVID-19 disease between 11.03.2020- 31.02.2021 in a Training and Research Hospital in İstanbul were included in the study. The sample of the study consisted of 32 patients out of 436 patients who met the sampling criteria. The data obtained by retrospective reviewing of the patient records were analyzed through the "Patient Information Form" and "Pressure Injury Stage" forms.

Results: Medical device-related pressure injury developed in 32 (7.3%) of 436 patients examined in the study on the specified dates. 90.6% of these patients were male, and the average age was 67.5. 43.7% had comorbid diseases. According to the Braden Risk Assessment Scale, 25% of these patients had medium and 71.8% high risk. Medical devices that cause pressure injury were continuous positive airway pressure mask (n=13), intubation tube (n=7), nasogastric tube (n=5), nasal cannula (n=3), gel pads (n=3), and oxygen mask (n=1).

Conclusion: In this study, the potential factors in the study that may have led to the incidence of medical device-related pressure injury specific to COVID-19 disease include the rapid increase in the need for respiratory support, ischemia caused by this infection, and the use of prone position.

Keywords: Pressure injury, respiratory support, prone position, intensive care

INTRODUCTION

Pressure injury is localized damage to the skin and/or subcutaneous soft tissue caused by the application of intense or prolonged pressure. Pressure injury is usually seen in tissues exposed to anatomical pressure in areas where the individual remains motionless, but it can also occur due to medical or other devices (1). Medical device-related pressure injuries are considered an important health problem for healthcare areas and are called hospital-acquired pressure injuries. Medical device-related pressure injuries occur when the skin or underlying tissues are exposed to constant pressure or shear from medical devices (1-3). All medical devices can potentially cause pressure injuries (4). Medical device-related pressure injuries generally occur around or below medical devices, taking the shape of the devices (2,5). Patients using medical devices are twice as likely to develop pressure injuries than patients who do not use medical devices (6). Medical device-related pressure injuries have been reported to account for more than 30% of all hospital-acquired pressure injuries (2,7).

It is known that acute respiratory failure develops in approximately 5% of patients infected with the COVID-19 disease caused by the coronavirus called SARS-CoV-2 and they need to be hospitalized in intensive care units (8). It has been described that the majority of these patients are over 60 years of age and have comorbidities such as hypertension, diabetes,

Corresponding Author: Tuna Ertürk, tunaerturk22@yahoo.com
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heart disease and obesity (9). All these factors pose a risk for the formation of pressure injuries. Besides, the increased need for respiratory support devices during intensive care treatment of COVID-19 disease becomes an important risk factor for pressure injuries caused by these devices (5-8). International and national guidelines such as the European Pressure Ulcer Advisory Panel (EPUAP), Wound Ostomy Continence Nursing (WOCN), National Pressure Injury Advisory Panel (NPIAP) have described care practices for pressure injuries related to medical devices, especially those associated with noninvasive respiratory support and pressure injuries related to the prone position (10-12).

The rates of intubation and mechanical ventilation among COVID-19 patients admitted to intensive care units have been reported as 71% to 90% (13). According to the studies examining medical device-related pressure injuries in these patients, these injuries may develop in the nasal and chin region, especially in patients receiving oxygen therapy with noninvasive respiratory support, and in the facial region connected to the intubation tube in patients who remain in the prone position for a long time (2,8,14).

A thorough examination of the evidence for pressure injury is essential in preventing pressure injuries. Observational studies including the incidence of medical device-related pressure injury, individual factors and care practices play an active role in ensuring patient safety. There are, however, limited studies on the prevalence of medical device-related pressure injuries. The aim of this study is to determine the prevalence of medical device-related pressure injuries in COVID-19 patients.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Hamidiye Clinical Researchs Ethics Committee (Date: 22.03.2021, Decision No: 21717). The study was conducted in compliance with the "Ethical principles for medical research involving human subjects" of the Helsinki Declaration.

This research was carried out with a cross-sectional and retrospective design. The data of 436 patients who were followed up and treated in the intensive care units of an anesthesia clinic with the diagnosis of COVID-19 between 11.03.2020 and 31.02.2021 in a training and research hospital in İstanbul were included in the study.

As inclusion criteria, the sample consisted of patients aged 18 years and over, who received respiratory support with low flow/high flow oxygen therapy or invasive/noninvasive mechanical ventilation, and who were reported to have developed medical device-related pressure injuries by wound care nurses. The individual and disease-related characteristics of 32 patients who met these criteria were examined for medical device-related pressure injury.

Data Collection Tools and Data Collection

Patients who received additional respiratory therapy in the intensive care unit from the first patient admitted to the hospital with the diagnosis of COVID-19 until the end of the year were identified. The data obtained by the retrospective scanning of patient files were examined through the "Patient Information Form" and "Pressure Injury Stage" form.

Patient Information Form

The form includes data on the individual and disease-related characteristics of pressure injury and the nursing care given for medical device-related pressure injury in line with the literature reviewed by the researchers (8-14). It covers the individual characteristics of the patients such as age, gender and body mass index (BMI). Among the features related to the disease are data such as respiratory support type, comorbid diseases such as diabetes mellitus (DM), hypertension, peripheral vasculopathy, pressure injury risk level according to Braden Risk Assessment Scale, date of onset of the pressure injury, injury sites.

Braden Risk Assessment Scale

The risk of pressure injury in the study was determined by the Braden Risk Assessment Scale. The scale was developed by Bergstorm et al. (16) with consideration to the pressure injury risk factors of patients and its Turkish validity and reliability were established by Oğuz and Olgun (Brad), The scale includes six risk factors: stimulus perception, humidity, activity, movement, nutrition, friction-irritation. Except for friction and shear, each variable is scored between 1 and 4. By summing the sub-dimension scores of the scale, a total score ranging from at least 6 to 23 is obtained. A total score of 12 points and below are considered as high risk, 13-14 points as risk, and 15-16 points as low risk.

Pressure Injury Stage Form

The stage of pressure injuries was evaluated according to the National Pressure Injury Advisory Panel (NPIAP) (17) (**Table 1**).

Data Analysis

Frequency and percentage descriptive statistics were used as methods of analysis, and categorical data analyzes were used for individual characteristics.

Table 1. Pressure Injury Stages (NPIAP)17
Stage 1 Pressure Injury: Non-blanchable erythema of intact skin Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin.
Stage 2 Pressure Injury: Partial-thickness skin loss with exposed dermis Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough and eschar are not present.
Stage 3 Pressure Injury: Full-thickness skin loss Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds.
Stage 4 Pressure Injury: Full-thickness skin and tissue loss Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining and/or tunneling often occur. Depth varies by anatomical location.
Unstageable Pressure Injury: Obscured full-thickness skin and tissue loss Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed.
Deep Tissue Pressure Injury: Persistent non-blanchable deep red, maroon or purple discoloration Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister. Pain and temperature change often precede skin color changes.

RESULTS

Pressure injuries due to respiratory support device developed in 32 (7.3%) of 436 patients examined on the set dates during the study. Of these patients, 90.6% were male, and the mean age was 64.65. 43.7% of them had comorbid diseases. The median value of the day of occurrence of pressure injury during the hospitalization period of the patients in the intensive care unit was found to be 6.5 days (**Table 2**). When the type of respiratory support received by 436 patients was examined, it was seen that 28% received treatment with low-flow oxygen, 27% with invasive mechanical ventilation, 23% with high-flow oxygen, and 22% with non-invasive mechanical ventilation (**Figure 1**). According to the Braden Risk Assessment Scale, 25% of these patients had medium risk and 71.8% high risk (**Figure 2**).

Table 2 also shows the data of the patients (n=32) who developed medical device-related pressure injury. Medical devices that caused pressure injury were mask providing positive pressure ventilation (n=13), intubation tube (n=7), nasogastric tube (n=5), nasal cannula (n=3), gel pad (n=3), and oxygen masks (n=1).

Stage I pressure injury behind the ear due to oxygen mask was reported in 1 patient who received low-flow oxygen therapy, and deep tissue damage behind the ear was reported in 3 patients who received high-flow oxygen therapy. In 13 (13.6%) of 95 patients who received respiratory support with Noninvasive Mechanical Ventilation (NIMV), mostly deep tissue damage was detected in the upper nose and chin region due to the NIMV mask. In 15 of 116 patients (12.9%) who received respiratory support with Invasive Mechanical Ventilation (IMV), medical device-related pressure injuries consisting of a nasogastric tube, gel pad and intubation tube were reported in various areas of the face (**Figure 3**). 78.12% of the injuries occurred were defined as deep tissue damage and 9.3% as unstageable stages (**Table 2**).

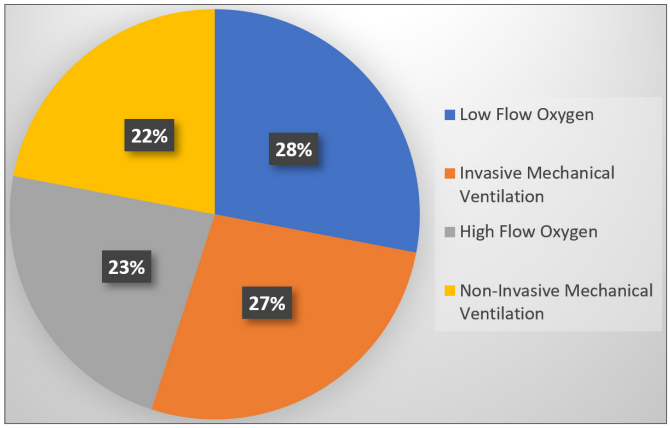

Figure 1. Ventilation support type of patients with medical device-related pressure injury

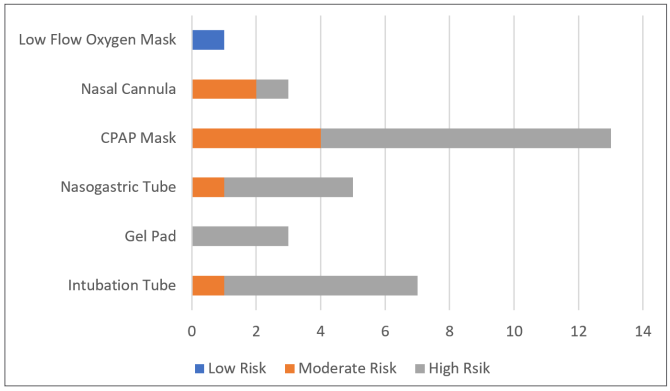

Figure 2. Medical devices that cause pressure injury according to the Braden risk level

*CPAP: Continious Positive Airway Pressure

Table 2. Characteristics of patients who develop medical device-related pressure injury.

Ventilation Support	Medical Device	Gender /Age	Comorbid	Braden Risk Level	Occur Date	1st Pressure Location/Stage	2nd Pressure Location/ Stage
LFOT	Mask	M/68	-	Low	3	Behind Left Ear/ 1	-
HFOT							
	Cannula	M/57	-	Moderate	10	Behind Right Ear/ DTPI	-
	Cannula	M/87	-	Moderate	6	Behind Right Ear/ DTPI	Behind Left Ear/ DTPI
	Cannula	M/64	-	High	6	Behind Right Ear/ DTPI	Behind Left Ear/ DTPI
NIMV							
	Mask	M/53	-	Moderate	2	Dorsal Nasal/DTI	-
	Mask	F/75	COPD	Moderate	8	Dorsal Nasal/DTPI	-
	Mask	M/58	-	Moderate	8	Dorsal Nasal/DTPI	-
	Mask	M/71	DM+HT	High	10	Dorsal Nasal/DTPI	-
	Mask	M/80	-	High	5	Dorsal Nasal/DTPI	-
	Mask	M/50	-	Orta	7	Dorsal Nasal/DTPI	Frontale/ DTPI
	Mask	M/68	-	High	3	Dorsal Nasal/2	-
	Mask	M/76	-	High	4	Mandibula/ DTPI	-
	Mask	M/49	-	High	7	Mandibula/ DTPI	-
	Mask	M/52	-	High	5	Mandibula/ DTPI	Upper Lip/DTPI
	Mask	M/53	DM+HT	High	3	Mandibula/ DTPI	-
	Mask	F/42	DM	High	7	Mandibula/ DTPI	-
	Mask	M/77	DM	High	9	Mandibula/ EE	-
IMV							
	NGT	M/78	HT	High	8	Dorsal Nasal/DTPI	-
	NGT	M/77	DM	High	4	Dorsal Nasal/DTPI	-
	NGT	M/84		High	5	Dorsal Nasal/DTPI	-
	NGT	F/80	Arrhythmia	Moderate	3	Dorsal Nasal/2	-
	NGT	M/85	DM	High	3	Dorsal Nasal/2	-
	Gel Pad	M/67	DM	High	20	Frontale/ DTPI	-
	Gel Pad	M/60	HT/CKD	High	6	Frontale/ DTPI	-
	Gel Pad	M/62	-	High	6	Frontale/ DTPI	-
	IT	M/68	CAD	High	5	Right Maxilla/ DTPI	Left Maxilla/DTPI
	IT	M/30		Moderate	4	Lower Lip/ DTPI	-
	IT	M/61	DM	High	9	Left Maxilla/ DTPI	Right Maxilla/DTPI
	IT	M/44	-	High	8	Mandibula/ EE	-
	IT	M/64	-	High	14	Mandibula/ EE	Upper Lip/ DTPI
	IT	M/59	HT+MI	High	4	Mandibula/ DTPI	Frontale/ DTPI
	IT	M/70	-	High	6	Mandibula/DTPI	-

*LFOT: Low Flow Oxygen Therapy, HFOT: Flow Oxygen Therapy, NIMV: Noninvasive Mechanical Ventilation, IMV: Invasive Mechanical Ventilation, NGT: Nasogastric Tube, IT: Intubation Tube, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, CKD: Chronic Kidney Disease, CAD: Coronary Artery Disease, DTPI: Deep Tissue Pressure Injury, UPI: Unstageable Pressure Injury

DISCUSSION

Acute respiratory failure syndrome is a common complication due to COVID-19 infection (18) and has thus led to an increase in the number of patients needing respiratory support in intensive care units, resulting in most of these patients receiving respiratory support with low/high flow oxygen therapy or invasive/noninvasive mechanical ventilation (19-21). Although the exact data are not yet available, it is known that the increase in the need for respiratory devices and the prone position given to increase oxygenation has caused a significant increase in the incidence of medical device-related pressure injury (2,12).

In our study, the prevalence of medical device-related pressure injury in 436 patients treated in the intensive care unit with the diagnosis of COVID-19 disease, which we examined over a 12-month period, was determined as 7.36% (n=32). The most common devices causing pressure injuries were positive pressure ventilation masks (40.6%) and intubation tubes (21.8%). Kayser et al. (22) reported the prevalence of medical device-related pressure injury as 0.6% (n=601) with the most common devices causing them being nasal cannula (26%) and masks providing positive pressure ventilation (9%), respectively. In an 11-month prevalence study conducted by Arnold-Long et al. (23), 47% (n=142) of the patients

developed medical device-related pressure injury, and the most common devices causing this were respiratory devices, intubation tubes, splints and fixations, respectively. In a study by Jackson et al. (24) in which the authors systematically compiled the data of twenty-nine studies (17 cross-sectional studies and 12 cohort studies) including data on 126.150 patients, the mean prevalence of medical device-related pressure injury was 10%. The most common medical devices causing these injuries were devices providing respiratory support, neck collars, tube connection cables, splints and intravenous catheters (25). The studies in the literature on medical devices-related pressure injuries seem to have limitations and differences. This may be because some nurses working in different institutions do not have sufficient knowledge about the terminology of the National Pressure Injury Advisory Panel (NPIAP) or do not agree with NPIAP about staging (17). The differences between pressure injury risk assessment scales may also be another reason. For example, the Glamorgan Scale, which is specific to pediatric patients, considers medical devices as pressure injury risk, whereas many of the commonly used scales to evaluate pressure injury risks in adults (e.g., Braden, Waterlow, etc.) disregard these devices (25). The prevalence determined in our study, i.e. 7.36%, seems to be below the average values compared to the literature. This may be due to the individual characteristics of the patients, the differences in the health care services they receive, and the fact that our sample consisted of patients who developed medical device-related pressure injury providing only respiratory support.

Of the 32 patients, 90.6% of whom were male, and the mean age was 64.64, who developed medical device-related pressure injury in the study, 43.7% had a history of comorbidity and a significant majority of these patients had high Braden Risk Scale scores. The study of Ibara et al. (26) evaluating pressure injuries due to prone position during the COVID-19 pandemic emphasized that the majority of patients who developed such injuries due to medical devices (72%) were male patients. In that study, the mean age of the evaluated patients was 61 and all had very high Braden Risk Scale scores (26). In another similar study conducted by Sleiwah et al. (18), the majority of the patients were male (87%), and the mean age was 58.6. In the study of Martel and Orgill (2), the majority of patients who developed medical device-related pressure injury were also male. Girard et al. (27) reported that being male and 60 years of age and older increased the risk of pressure injury in a study they conducted to evaluate the effect of the position given to the patient on pressure injury in patients with acute respiratory failure. Most patients treated in intensive care units are at high risk of developing pressure injury due to insufficient tissue perfusion, being sedated and restricted in their ability to move, as well as having a history of comorbidities. Added to these factors, the use of medical devices further increases the risk of medical device-related pressure injury, and among the devastating effects of COVID-19, cytokine release syndrome and cytokine storm, endothelial dysfunction and ischemia accelerate the pressure injury process (2,18,28). Determining the age, gender, comorbidities, and most importantly, the risk level of medical device-related pressure injury in the care of patients receiving respiratory support and meeting their care needs by taking into consideration the risk factors can be deemed a prerequisite to prevent the development of pressure injuries, including pressure injuries, due to medical devices.

In our study, when the findings related to the areas where pressure injuries developed due to medical devices were examined, it was observed that pressure injuries developed mostly on the nose (37.5%) and chin (31.25%). Among the pressure injury stages, deep tissue damage was found to have the highest prevalence. In the study of Ibarra et al. (26), the cheek (18%), upper nose (18%) and chin (16%) were the most affected areas, and the prevalence of Stage 2 pressure injury was the highest (64%), followed by Stage 1 pressure injury. In the study of Sleiwah et al. (18), the prevalence of medical device-related pressure injury was most common around the mouth and the prevalence of stage 2 pressure injuries was the highest, followed by stage 3 and unstaged pressure injuries. We believe that the more common prevalence of deep tissue damage and unstaged pressure injury in medical device-related pressure injury in our study compared to previous studies may be related to the prone positioning of the majority of patients for a long time in order to increase oxygenation for the management of severe acute respiratory failure and the increase in the pressure applied by the medical devices to the tissue. We also believe that the difficulty of working with protective equipment during the COVID-19 pandemic process, the insufficient number of nurses and lack of training, the fact that the newly assigned nurses in the intensive care units do not have sufficient knowledge about medical device-related pressure injury may be related to these findings of our study (27-29). Current international guidelines recommend that comprehensive evaluation of skin tissue under a medical device be performed regularly and documented in the patient's medical record (1,3,10-12). Evaluation of the tissue involves moving the device in place to dissipate the pressure the tissue is exposed to. According to Sleiwah et al. (5), failure to choose the appropriately sized safety bands for the patient causes pressure injury. It is therefore imperative to apply the device correctly and choose the right size for the patient. In addition, we are of the opinion that the use of pressure sensors that will give warning signals in the application of

medical devices will be an effective method in preventing medical device-related pressure injury, especially during the COVID-19 pandemic, where workforce management is very important (5).

CONCLUSION

In our study, potential factors that may have caused the incidence of medical device-related pressure injury specific to COVID-19 disease include the rapid increase in the need for respiratory support, the ischemia caused by this infection, and the use of prone position. On the other hand, it can be said that the reasons such as lack of personnel against the increase in the demand for intensive care units, lack of education about pressure injury, limitations in accessing wound care materials, difficulties in the working environment under pandemic conditions may have increased the risk of pressure injury caused by medical devices.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Hamidiye Clinical Researchs Ethics Committee (Date: 22.03.2021, Decision No: 21717).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Assessment of carotid-intima media thickness in patients with epilepsy receiving antiepileptic drugs

Mehtap Kocatürk[1], Özcan Kocatürk[2]

[1]Balıkesir University, Department of Neurology, Balıkesir, Turkey
[2]Balıkesir Atatürk City Hospital, Department of Neurology, Balıkesir, Turkey

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ABSTRACT

Aim: This study aims to investigate whether there is an increase in carotid-intima media thickness (C-IMT) in epilepsy patients using antiepileptic drugs when compared to the normal control group and whether there is a difference when we group them as monotherapy and polytherapy.

Material and Method: 68 people were included in the prospective cross-sectional study. 38 epilepsy and 30 healthy control groups that were matched in terms of demographic characteristics

Results: C-IMT was statistically higher in the epilepsy group ($p<0.001$). When carotid USG results are analyzed as control, monotherapy, and polytherapy, there was no difference between control and monotherapy, there was statistical significance between the control group and polytherapy ($p<0.001$), and between monotherapy and polytherapy (p:0.010)

Conclusions: According to our study result, polytherapy should be avoided as much as possible, especially in patients with vascular risk factors.

Keywords: Carotid-intima media thickness, epilepsy, monotherapy-polytherapy

INTRODUCTION

Epilepsy affects 65 million people worldwide and is among the most common neurological diseases (1). Treatment is based on long-term anti-epileptic drugs (AEDs) and the use of these drugs is sometimes lifelong. Treatment aims to try to ensure seizure-freeness with drugs while minimizing the side effects of these drugs. Therefore, the physician should have a good knowledge of the side-effect profile of the drugs and know-how to manage the side-effects when they develop.

Long-term use of AEDs is associated with chronic adverse events such as metabolic and endocrine disorders, organ toxicity, cognitive dysfunction, and psychiatric problems (2-5). Studies have reported that patients with epilepsy have earlier deaths from stroke and ischemic heart disease compared to the general population (6,7). Although the reason for this relationship cannot be fully explained, it is thought that drugs may be responsible for this situation along with the disease itself. One of the reasons why mortality rates are higher than the general population may be susceptibility to atherosclerosis.

The impact of AEDs on the development of atherosclerosis has been discussed for a long time. The role of drugs in the pathogenesis of atherosclerosis has not been fully elucidated. Studies are showing that especially old generation antiepileptic drugs can cause dyslipidemia and hyperhomocysteinemia, which may lead to the development of atherosclerosis (8,9). In addition, inflammation marker CRP, which is closely related to atherosclerosis, and oxidative stress markers were detected in epilepsy patients using AED (10). There is also one opinion that atherosclerosis may be involved in the etiology of chronic cognitive dysfunction observed in epilepsy patients (11).

Carotid-intima media thickness (C-IMT) is an early marker of atherosclerosis and its increase is a predictor of future vascular events. Although they have controversial results, studies are showing that C-IMT increase in epilepsy patients (12,13). In this study, we aim to investigate whether there is an increase in C-IMT in epilepsy patients using antiepileptic drugs when compared to the normal control group and whether there is a difference when we group them as monotherapy and polytherapy.

Corresponding Author: Mehtap Kocatürk, mehtap-3381@hotmail.com
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MATERIAL AND METHOD

The study was approved by the Harran University Faculty of Medicine Ethics Committee (Date: 08.07.2019, Decision No: 07-13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This cross-sectional study included 68 subjects, 38 epilepsy who were taking one or more antiepileptic drugs, and 30 healthy control. The study was conducted from June 2019 to September 2019 at the Neurology Department of Harran University Hospital. Exclusion criteria are including patients under 18 and over 50, body mass index above 35, hyperlipidemia, known heart disease, hypertension, diabetes mellitus, oral contraceptive usage, history of the previous stroke, multiple sclerosis, and inflammatory disease. Patients were also excluded from the study if the epilepsy was caused by metabolic or neurodegenerative diseases and taking any medication or vitamin preparations other than antiepileptic drugs. Patients were selected from those diagnosed as having epilepsy according to the International League Against Epilepsy (ILEA) 2017 criteria and who were using one or more antiepileptic drugs in treatment (14). The diagnosis of epilepsy made by an experienced neurologist (M.K.), was based on the clinical history, including the response to medication, seizure description, and electroencephalography, and magnetic resonance imaging result. The control group consisted of individuals of the same age, sex, and BMI without a history of epilepsy. The physical and neurological examinations of the control group were normal. Written informed consent was obtained from the patients before being included in the study. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure 90 mmHg, and/or taking antihypertensive medication, and/or a history of diagnosed hypertension. Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dL (7 mmol/L), non-fasting glucose ≥200 mg/dL (11.1 mmol/L), use of diabetic medications, or a previously established diagnosis. Hyperlipidemia was defined as low-density lipoprotein > 160 mg/dL, and/or taking a lipid-lowering agent.

Bilateral carotid arteries USG examination was done by the same neurologist (Ö.K. with 7 years of US experience and were blinded to epilepsy diagnosis and clinical data). The examinations were performed using the LOGIQ V5 (GE Medical Systems, Wuxi, China) with the same linear-array transducers. In the supine position, bilateral common and internal carotid arteries were examined for the presence of atherosclerotic plaques, using grayscale and color Doppler modes. C-IMT was defined as the thickness of the hypoechoic layer between the vessel lumen and hyperechoic adventitia. C-IMT was measured in the posterior walls of both left and right CCA at 1 cm below the carotid bifurcation outside the areas of plaque and the average of two values (right wall and left wall) was recorded as C-IMT mean.

Statistical Analyses

The parameters were analyzed using SPSS for Windows ver. 23.0. Continuous variables are expressed as the mean±standard deviation and categorical variables as numbers and percentages. The Mann–Whitney U test was used to assess the differences between continuous variables in two groups. The Kruskal–Wallis test was used to compare more than two independent groups. Correlation between continuous variables was evaluated with the Spearman correlation test. The chi-square test was used to analyze categorical parameters and $p < 0.05$ was considered statistically significant.

RESULTS

This study compared healthy control (n=30; mean age 27.57±6.10 years) and epilepsy (n=38; mean age 25.58±7.61 years) groups. There were no significant intergroup differences in age, percentage of sex, serum lipid level, or BMI (**Table 1**).

Table 1. Demographic and clinical findings of the epilepsy patient and control groups

	Epilepsy n :38	Control n: 30	p
C-IMT	0.46 (±0.08)	0.37 (±0.04)	0.000
Age (years)	25.58 (±7.61)	27.57 (±6.10)	0.248
Female, n (%)	24 (55.8)	19 (44.2)	0.595
BMI (kg/m^2)	23.29 (±4.38)	24.15 (±3.52)	0.381
Epilepsy type (ILEA-2017)			
Focal onset	24 (63.2)		
Generalized onset	10 (26.3)		
Unknown Onset	4 (10.4)		
Seizure etiology, n (%)			
Structural	12 (31.6)		
Genetic	10 (26.3)		
Unknown	16 (42.1)		
Disease duration (years)	7.84 (±5.82)		
Number of AED			
Monotherapy	16 (42.1%)		
Polytherapy	22 (57.9%)		
Serum lipid level (mg)			
LDL cholesterol	107.73 (±16.45)	99.62 (±14.20)	0.201
HDL cholesterol	60.39 (±15.11)	53.82 (±14.60)	0.074
Triglyceride	100.59 (±36.55)	109.08 (33.28)	0.521

C-IMT: Carotid intima media thickness, BMI: Body Mass Index
AED: Anti Epileptic Drug, LDL:Low Density Lipoprotein HDL: High Density Lipoprotein

The patients were diagnosed as having focal epilepsy in 24 (63.2%), generalized epilepsy in 10 (26.3%) cases, and unknown in 4 (10.4%). Of the patients in the study group, 16 (42.1%) were receiving monotherapy and 22 (57.9%)

were receiving polytherapy. Eighteen of the patients in the polytherapy group were taking double antiepileptic, and 4 were taking triple antiepileptic. Considering the etiology of seizures, 12 (31.6%) patients are structural, 10 (16.3%) patients are genetic, and the etiology of 16(42.1%) patients is unknown.

When the study population was analyzed as monotherapy (n=16; mean age 23.88±7.32 years), polytherapy (n=22; mean age 26.82±7.73 years), and control groups (n=30; mean age 27.57±6.10 years), there was no difference between the groups in terms of age, gender, BMI and serum lipid levels (**Table 2**).

When carotid ultrasound findings were compared between epilepsy and control groups, C-IMT was statistically higher in the epilepsy group(p<0.001)(**Table 1**). When carotid USG results are analyzed as control, monotherapy, and polytherapy, there was no difference between control and monotherapy, there was statistical significance between the control group and polytherapy (p<0.001), and between monotherapy and polytherapy (p:0.010) (**Table 2**). Distribution of antiepileptic drugs used by the patients were showed in **Table 3**. **Figure 1** showed that there was no relationship between the duration of epilepsy and the increase in C-IMT.

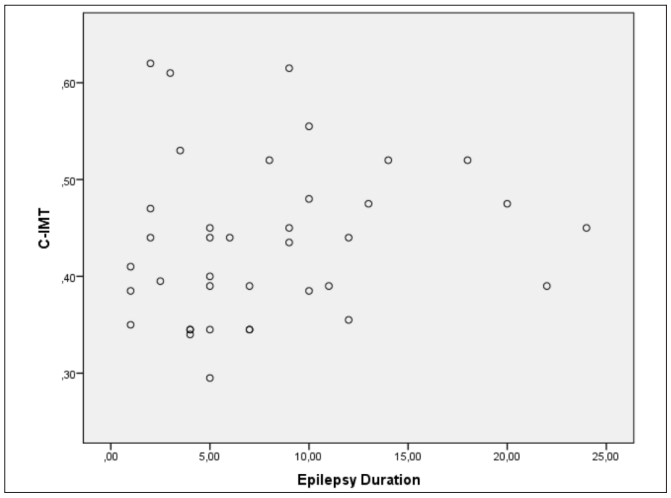

Figure 1. Correlation between epilepsy duration and C-IMT (p:0.217). C-IMT: Carotid-intima-media thickness

Table 3. Distribution of antiepileptic drugs used by the patients

	Monotherapy (n)	Polytherapy(n)	Total (n)
Levetirecetam	6	13	19
Lamotrigine	2	11	13
Valproic acid	5	9	14
Carbamazepine	3	10	13
Topiramate	-	2	2

DISCUSSION

C-IMT measurement is a noninvasive ultrasonographic method and is applied easily and inexpensively (12). Its increase is indicative of subclinical atherosclerosis and is associated with many vascular events, including cardiovascular and cerebrovascular accidents (15). Although there are studies evaluating whether there is an increase in C-IMT in epilepsy patients using antiepileptic drugs, according to our knowledge, there is no study evaluating the increase in C-IMT in adult patients according to polytherapy-monotherapy groups. In this study, we planned to investigate whether the use of polytherapy has an effect on the increase in C-IMT and we obtained statistically significant results. In our study, we examined whether there was a significant difference in C-IMT between 30 healthy controls and 38 epilepsy patients, who were matched in terms of age, sex, and BMI. As a result, it was seen that there was a statistically significant C-IMT increase in the patient group compared to the control group (**Table 1**).

When we divided epilepsy patients as monotherapy and polytherapy, the increase in CIMT in the polytherapy group was statistically significant compared to the monotherapy group. However, when monotherapy and healthy control groups were compared, the result did not reach statistical significance (**Table 2**). In our study, the disease duration did not affect CIMT (**Figure 1**)

The results of C-IMT studies in epilepsy patients are controversial due to the diversity of patient groups (age, therapy, comparison vb.). In one study, while an increase in CIMT was observed in epilepsy patients compared to the healthy control group, the same study did not find a significant difference between patients taking valproic acid

Table 2. C-IMT, Age, BMI, LDL, HDL, Triglyceride mean values±standard deviation of Control, Monotherapy and Polytherapy groups.

	Control (n:30)	Monotherapy (n:16)	Polytherapy (n:22)	P values	P1	P2	P3
C-IMT	0.37 (±0.04)	0.40 (±0.08)	0.46 (±0.08)	<0.001	0.35	<0.001	0.01
Age (years)	27.57 (±6.09)	23.88 (±7.32)	26.82 (±7.73)	0.227	-	-	-
Female, n (%)	19 (63.3%)	10 (62.5%)	14 (63.6%)	0.997	-	-	-
BMI (kg/m²)	24.16 (±3.52)	22.44 (±4.28)	23.91 (±4.44)	0.371	-	-	-
Serum lipid level (mg)							
LDL cholesterol	99.62 (±14.20)	103.06 (±30.51)	111.18 (±30.64)	0.275	-	-	-
HDL cholesterol	53.82 (±14.46)	58.44 (±13.92)	58.44 (±13.93)	0.162	-	-	-
Triglyceride	109.08 (33.28)	93.00 (±33.23)	105.9 (±35.83)	0.629	-	-	-
Disease duration (years)		5.71 (±5.29)	9.39 (±5.80)	0.054			

P: within groups, P1: significance between control-monotherapy, P2: significance between control-polytherapy. P3: significance between monotherapy and polytherapy,

and enzyme-inducing drugs (16). In a meta-analysis of 15 studies involving 1175 epileptic patients, the majority of epilepsy patients using AEDs had increased C-IMT (15).

Among AEDs, especially CBZ and VA were more significantly associated with the increase in C-IMT. While phenytoin had no significant effect on C-IMT, studies about LMT were inconclusive. The results of phenytoin were attributed to study group smallness and heterogeneity. In our study, there was no difference between the groups in terms of lipid profile, and the increase in C-IMT was independent of lipid level. In the literature, some studies are compatible with this study (10,17), as well as studies that correlate with lipid increase (18). The effect of treatment duration on CIMT is controversial. While studies are stating that the duration is independently effective on the increase in C-IMT (18,19), there are also studies stating that it does not have any effect (10,16,20). We could not evaluate the duration of treatment because we had polytherapy patients in the study group. We looked at the duration of epilepsy in our patients. In our study, the duration of epilepsy did not affect C-IMT.

When evaluating the increase in C-IMT in epilepsy patients, most of the studies included patients receiving monotherapy and analyses were made on specific drug groups. On the other hand, we divided the patients into monotherapy and polytherapy instead of a group using a certain drug. Similar to our study, Çalık et al. (18) made a distinction between monotherapy and polytherapy in pediatric patients and found the increase in C-IMT compatible in our study.

In addition, since epilepsy patients who did not use drugs were not included in the studies, it was interpreted that it could not be determined whether atherosclerosis was caused by the disease itself or the drugs used (16). When we separate and evaluate our patients as monotherapy and polytherapy, there is no difference between the monotherapy group and the control group in terms of C-IMT increase, but the fact that the polytherapy group is significant compared to the monotherapy group may highlight the effect of drugs rather than the disease. There is a need to work with larger patient groups for stronger comments on this issue. The limitations of our study are its cross-sectional nature and heterogeneous drug use in our patients.

CONCLUSION

According to our study results, it may be recommended to closely monitor atherosclerotic risk factors to prevent future vascular events, especially in epilepsy patients receiving polytherapy, however, more research is needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Harran University Faculty of Medicine Ethics Committee (Date: 08.07.2019, Decision No: 07-13)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: The authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Long term outcomes of patients who underwent radical hsyterectomy for cervical cancer

Ahmet Bilgi[1], Mete Can Ateş[1], Havva Hande Keser Şahin[2], Fazıl Avcı[1], Abdül Hamid Güler[1], Mehmet Kulhan[1], Ersin Cintesun[1], Çetin Çelik[1]

[1]Selçuk University Faculty of Medicine, Department of Gynecology and Obstetrics, Konya, Turkey
[2]Hitit University Faculty of Medicine, Department of Pathology, Çorum, Turkey

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ABSTRACT

Introduction: We aimed to examine the parameters affecting long-term prognosis and survival in patients diagnosed with early stage cervical cancer and undergoing radical hysterectomy in our Gynecology and Obstetrics Clinic.

Material and Method: The files of 86 cervical cancer patients who underwent radical hysterectomy and pelvic paraaortic lymph node dissection for cervical cancer between 2010 and 2021 were retrospectively reviewed. Tumor size, FIGO stage, vagina, endometrium, ovary, parametrium, pelvic lymph node, paraaortic lymph node and deep stromal involvement were examined by examining the files and pathology reports of the patients. Then, the effects of these parameters on pelvic and paraaortic lymph node involvement, postoperative prognosis and survival of the patients were tried to be revealed.

Results: The 86 patients included in the analysis had a mean age of 55.2 (range: 38-72) and a median tumor size of 35 mm (range: 2-74). Cell type was squamous cell carcinoma in 81.4% and adenocarcinoma in 18.6% of the patient group. During the follow-ups, recurrence was detected in 22 (25.6%) patients. During the follow-up period, it was found that 18 (20.9%) patients died. In univariate analysis, the presence of metastases in any lymph node was found to reduce DFS and OS. The mean follow-up period of the cases examined was 66 (min:12-max:132) months; The mean OS and DFS of the patients were 111.84 (95% CI:103.26-120.43) and 105.72 (95% CI:95.87-115.57) months, respectively.

Conclusion: Pelvic and paraaortic lymph node involvement was found to be the most important prognostic factor regardless of histological type in cervical cancers. Survival was found to be significantly lower in patients with any lymph node involvement.

Keywords: Cervical cancer, radiotherapy, radical hysterectomy, prognostic factor, survival

INTRODUCTION

According to 2018 GLOBOCAN data, cervical cancer ranks fourth worldwide after breast, colorectal and lung cancers. The frequency order rises to the second rank in socioeconomically backward countries (such as South America and Africa) (1). Cervical cancer death rates have decreased in the last few decades due to the widespread application of cytology screening, advances in classical surgical methods, the introduction of new instruments and medical technologies, and the spread of chemoradiotherapy. However, more than 265,000 women die from cervical cancer each year (2). Cervical cancer staging was classically determined by clinical examination according to the International Federation of Gynecology and Obstetrics (FIGO) (3). However, FIGO proposed a modification in 2018 that included the use of imaging methods and postoperative pathological examination in order to perform more detailed staging (4). Cervical cancer treatment plan varies according to the stage at diagnosis. Cure can be achieved with surgery (alone or by adding radiotherapy) in early stage cervical cancers (Stage I-IIa) (5). In the Surveillance, Epidemiology, and End Results (SEER) database, 5-year survival rates for cervical cancer were reported as 91.8% for localized disease and 56.3% for locally advanced disease and 15% for metastatic cases between 2008 and 2014 (6). Life expectancy of cancer patients has increased both in the world and in our country, thanks to new treatment opportunities (7). In recent years, numerous studies have investigated the relationship between 5-year survival rates of women with cervical cancer and various treatment modalities, including radical hysterectomy (8, 9). Most of these studies have focused on general trends in survival rates without investigating the clinical and pathological aspects and and only a few reports have discussed the long-term observation of these patients. In this study, we aimed to examine the clinical

Corresponding Author: Ahmet Bilgi, abilgi77@gmail.com
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and pathological aspects of the parameters affecting the prognosis and 10-year disease-free survival (DFS)-overall survival (OS) in patients diagnosed with cervical cancer and undergoing radical hysterectomy in our Gynecology and Obstetrics Clinic.

MATERIAL AND METHOD

Ethics committee approval for the study was obtained from Ethics Committee of Selçuk University (Date: 21.04.2021, Meeting no: 2021/08, Decision no: 2021/214). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The records of 86 patients who were diagnosed with cervical cancer and underwent surgical treatment in the Gynecology Oncology Clinic of our university between January 2010 and February 2021 were reviewed retrospectively. Exclusion criteria from the study were: not attending follow-ups, going to another center for treatment after diagnosis, and having other accompanying gynecological or non-gynecological malignancies. The data of the patients were analyzed retrospectively. The preoperative diagnosis was based on the histopathologic examination of tissue obtained from cervical biopsy and fractionated abrasion. Patients were staged using the FIGO 2018 clinical staging system based on vaginal speculum examination, bimanual examination, and rectal examination. Early-stage cervical cancer refers to FIGO stage IA, IB1, and IB2 disease. The patients were evaluated with imaging methods (computed tomography, magnetic resonance imaging) at the time of diagnosis. All patients underwent radical hysterectomy and pelvic + paraaortic lymphadenectomy. By examining the demographic data and pathology reports of the patients, tumor size, FIGO stage, vagina, endometrium, ovary, parametrium, pelvic lymph node, paraaortic lymph node, deep stromal involvement were examined. After the operation, the patients were surgically staged. After the postoperative recovery period, radiotherapy was applied to 47 patients (54.7%). Then, the effects of these parameters on pelvic and paraaortic lymph node involvement and the postoperative prognosis and survival of the patients were tried to be revealed. Relapse development and it's treatment, 10-year DFS, and OS were analyzed. The patients were checked every 3 months for the first 2 years, every 6 months for the next 2 years, and annually in the following years. Pelvic examination, whole abdomen ultrasonography imaging and complete blood count were performed at each control. Abdominal and thorax tomography was performed annually for scanned metastasis. DFS was taken as the time interval from the time of diagnosis to recurrence or to the last follow-up visit. OS was taken as the time interval from the time of diagnosis to the date of the last examination or the date of death.

Statistical Evaluation

Survival analyzes were performed using the Kaplan-Meier method and the results were compared with the log-rank test. Cox regression analysis was used to evaluate risk factors. Chi-square and Fisher tests were used to compared proportions. Student-t test was used to compared parametric continuos variables. All statistical analyzes were performed with the Statistical Package for the Social Sciences (SPSS) program. $p < 0.05$ was considered statistically significant.

RESULTS

The 86 patients included in the analysis had a mean age of 55.2 (range: 38-72) and a median tumor size of 35 mm (range: 2-74). Tumor size was ≤20 mm in 53.5%, >20 - ≤40 mm in 32.6%, and >40 mm in 14% of patients. Cell type was squamous cell carcinoma in 81.4% and adenocarcinoma in 18.6% of the patient group. General characteristics study group were shown in **Table 1**. Mean follow-up was 66.84 (SD 37.16) months (range: 12-132). During the follow-ups, recurrence was detected in 22 (25.6%) patients. It was observed that 60.8% of these recurrences developed in the first year, and 78.9% within 3 years. Only pelvic recurrence was observed in all of the patients, and no long-distance recurrence was observed. The mean time from radical surgery to recurrence was 20.3 months (range: 4-72; median: 11). During the follow-up period, it was found that 18 (20.9%) patients died. All deaths occurred within 3 years. Mean duration from radical surgery to death was 28.1 months (range: 12-32; median:18).

In univariate analysis, the presence of metastases in any lymph node was found to reduce DFS and OS (**Table 3** and **Table 4**). In multivariate analysis, factors that were found to be significant in univariate analysis were evaluated and it was determined that although the presence of metastases in any lymph node reduced both DFS and OS times, there were no statistically independent prognostic factors. This situation contradicts the literature and is associated with the low number of cases (**Table 3** and **Table 4**).

The mean follow-up period of the cases examined was 66 (min:12-max:132) months; The mean OS and DFS of the patients were 111.84 (SD 16.12) (95% CI:103.26-120.43) and 105.72 (SD 17.09) (95% CI:95.87-115.57) months, respectively. (**Figure 1** and **Figure 2**). When 10-years OS according to the histology results of the patients examined within the scope of the study is considered, the average OS time of those with squamous cell cancer was 112.6 (SD 4.88) (95% CI:102.62-132.47) months, while the average survival time in other histological types was 104.25 (SD 9.27) (95% CI:97.78-124.71) months. There was no statistically significant difference in terms of DFS and OS between those with squamous cell cancer and other histological types (p=0.631, p=0.868) (**Table 2**).

Table 1. Characteristics of the study population

	N (%)
Age; years, mean ± standard deviation	55.2±10.7
Menopausal status	
Premenopause	27 (31.4)
Postmenopause	59 (68.6)
Histological subtype	
Squamous	70 (81.4)
Adenocarcinoma	16 (18.6)
FIGO STAGE (2018)	
Stage IA1	13 (15.1)
Stage IA2	4 (4.7)
Stage IB1	15 (17.4)
Stage IB2	22 (25.6)
Stage IB3	14 (16.3)
Stege IIA1	5 (5.8)
Stage IIA2	-
Stage IIB	2 (2.3)
Stage IIIA	-
Stage IIIB	-
Stage IIIC1	7 (8.1)
Stage IIIC2	4 (4.7)
Stage IVA	-
Stage IVB	-
Tumor size	
≤ 2 cm	46 (53.5)
>2 - ≤ 4 cm	28 (32.6)
> 4 cm	12 (14)
Depth of invasion	
<%50	77 (89.5)
≥%50	3 (3.5)
Full thickness invasion	6 (7)
LVSI	
No	72 (83.7)
Yes	14 (16.3)
Parametrial involvement	
No	82 (95.3)
Yes	4 (4.7)
Vaginal involvement	
No	79 (91.4)
Yes	7 (8.1)
Perineural invasion	
No	81 (94.2)
Yes	5 (5.8)
Lymph node involvement	
No	84 (97.7)
Yes	2 (2.3)
Surgery	
Type 1 Hysterectomy	12 (14)
Type 2 Hysterectomy	62 (72.1)
Type 3 Hysterectomy	12 (14)
Treatment	
Only surgery	39 (45.3)
RT	35 (40.7)
RT+Brachiaterapy	12 (14)
Recurrence	
No	64 (74.4)
Yes	22 (25.6)
Status	
Alive	68 (79.1)
Death	18 (20.9)

RT: radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

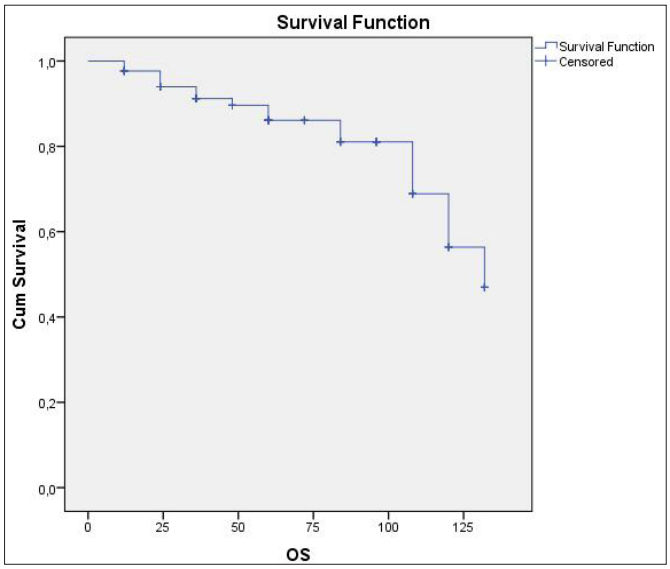

Figure 1. OS for all patients

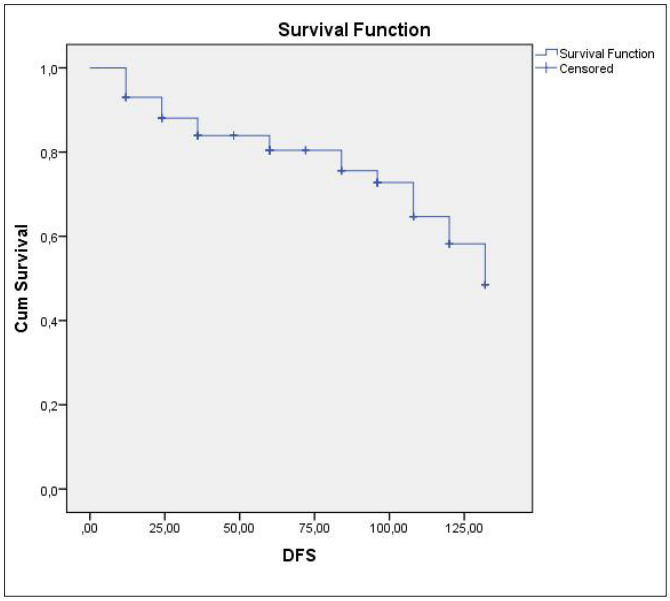

Figure 2. DFS for all patients

The mean OS of those without parametrial involvement was 113.15 (SD 4.44) (95% CI:108.66-132.47) months, and the mean DFS was 108.23 (SD 5.01) (95% CI:97.58-119.01) months. In those with parametrial involvement, the same parameters were 90 (SD 22.04) (95% CI:89.0-108.0), 60 (SD 22.65) (95% CI:59.35-86.64) months, respectively (**Table 2**). A statistically significant difference was found between 10-year DFS and OS rates according to parametrial involvement (p=0.007, p=0.05). A statistically significant difference was found between 10-year OS and DFS rates according to lymph node involvement (p<0.05, p<0.05, respectively). The 10-year OS and DFS rate of patients without lymph node involvement was significantly higher than those with lymph node involvement. (**Figure 3-6**).

Table 2. Result of Kaplan-Meier survival analysis

	N (%)	DFS (Mean)	p	OS (Mean)	p
Menopausal status					0.149
Premenopause	27 (31.4)	94.83±8.71	0.725	94.83±8.71	
Postmenopause	59 (68.6)	106.83±5.86		115.93±4.51	
Histological subtype					0.631
Squamous	70 (81.4)	104.89±5.78	0.868	112.6±4.88	
Adenocarcinoma	16 (18.6)	104.25±9.27		104.25±9.27	
FIGO STAGE (2018)					0.001
Stage I	54 (62.8)	116.52±5.69	0.005	122.73±4.51	
Stage II	19 (22)	100.92±11.9		108.63±10.36	
Stage III	13 (15.1)	78.31±11.94		80.54±11.81	
Stage IV	-				
Depth of invasion					
<%50	77 (89.5)				
≥%50	3 (3.5)	censored		censored	
Full thickness invasion	6 (7)	censored		censored	
LVSI					0.767
No	72 (83.7)	106.34±5.29	0.57	111.81±4.63	
Yes	14.8(16.3)	100.45±14.73		108.55±13.02	
Vaginal involvement					0.312
No	79 (91.9)	105.28±5.33	0.737	110.3±4.79	
Yes	7 (8.1)	98.68±15.9		96±5.19	
Perineural invasion					0.334
No	81 (94.2)	107.9±5.06	0.097	113.04±4.43	
Yes	5 (5.8)	70.8±19.02		88.5±15.09	
Parametrial involvement					0.05
No	82 (95.3)	108.23±5.01	0.007	113.15±4.44	
Yes	4 (4.7)	60±22.65		90±22.04	
Pelvic lymph node involvement					0.02
No	78 (90.7)	109.09.21±5.19	0.05	115.75±4.37	
Yes	8 (9.3)	83.5±11.85		86.5±11.45	
Paraaortic lymph node involvement					0.03
No	84 (97.7)	113.74±4.23	0.01	127.96±2.28	
Yes	2 (2.3)	42±6		48±0	
Surgery					0.449
Type 1 Hysterectomy	12 (13.9)	122.4±8.58	0.207	122.4±8.58	
Type 2 Hysterectomy	62 (72.2)	99.97±6.48		108.65±5.61	
Type 3 Hysterectomy	12(13.9)	102.37±3.34		105±3.96	
Treatment					
Only surgery	39 (45.3)	124.96±3.99	0.01	censored	
ERT	35 (40.7)	91.54±8.55		-	
ERT+Brachiaterapy	12 (14)	70±10.52		censored	

OS: overall survival, DFS: disease free survival, ERT:External radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

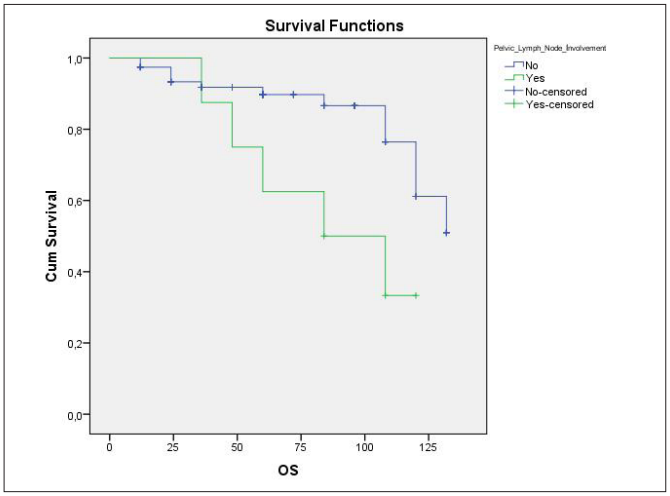

Figure 3. OS according to pelvic lymph node involvement

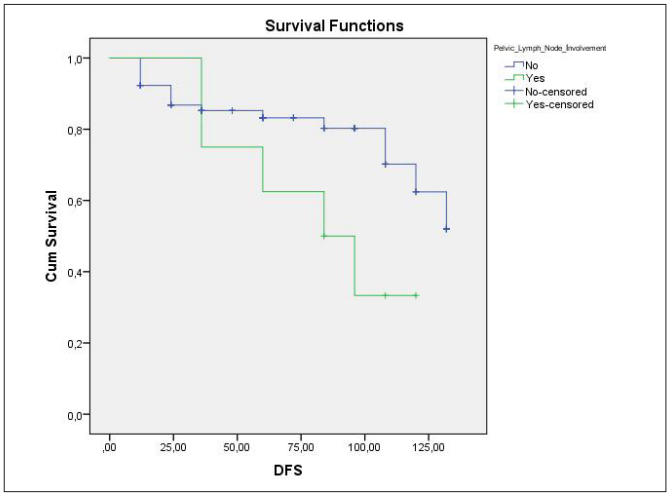

Figure 4. DFS according to pelvic lymph node involvement

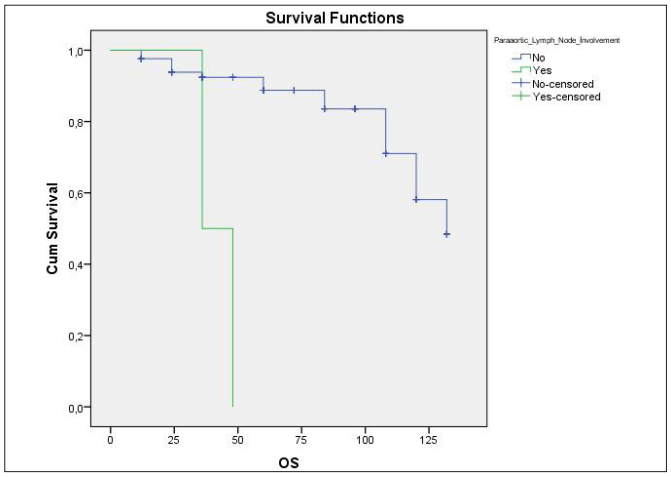

Figure 5. OS according to paraaortic lymph node involvement

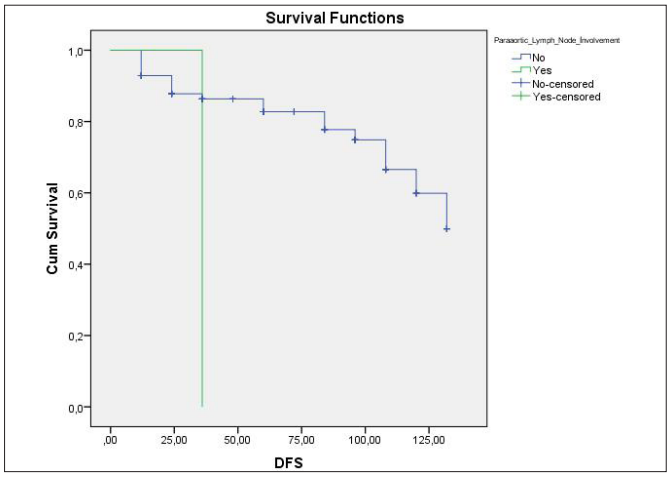

Figure 6. DFS according to paraaortic lymph node involvement

Table 3. Univariate and Multivariate Analysis of Potential Prognostic Factors for OS

	UNIVARIATE			MULTIVARIATE		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age (years)	0.969	0.927-1.014	0.175			
Hystologic type						
Squamous			Reference			
Adenocarcinoma	1.311	0.423-4.058	0.639			
Menopausal status						
Premenopause			Reference			
Postmenopause	0.486	0.175-1.344	0.164			
Tumor diameter						
≤ 2 cm			Reference			
> 2 cm	0.896	0.355-2.26	0.815			
FIGO Stage						
I			Reference			
II	1.58	0.405-6.171	0.05	2.77	0.689-11.14	0.151
III	6.19	2.047-18.74	0.04	7.68	1.98-29.74	0.003
IV	-	-	-			
Parametrial involvement						
No			Reference			
Yes	2.97	0.668-13.2	0.21			
Depth of invasion						
<%50			Reference			
≥%50	0.001	0.001-0.001	0.985			
Full thickness invasion	0.678	0.9-5.12	0.706			
LVSI						
No			Reference			
Yes	1.18	0.385-3.61	0.772			
Vaginal involvement						
No			Reference			
Yes	2.354	0.237-23.411	0.465			
Perineural invasion						
No			Reference			
Yes	2.01	0.458-8.81	0.355			
Pelvic lymph node involvement						
No			Reference			
Yes	3.137	1.1-8.49	0.03	1.198	0.043-0.922	0.03
Paraaortic lymph node involvement						
No			Reference			
Yes	13.16	2.64-65.47	0.002	6.562	0.366-128.269	0.215
Surgery						
Type 1 Hysterectomy			Reference			
Type 2 Hysterectomy	3.02	0.399-22.92	0.284			
Type 3 Hysterectomy	1.89	0.169-21.22	0.604			
Adjuvan Terapy						
Only surgery			Reference			
ERT	7.138	2.01-25.27	0.002			
ERT+Brachiaterapy	0.001	0.001-0.001	0.979			

OS: overall survival, HR: hazard ratio, CI: confidence interval, ERT: External radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

Table 4. Univariate and Multivariate Analysis of Potential Prognostic Factors for DFS

	UNIVARIATE			MULTIVARIATE		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Age (years)	0.988	0.95-1.028	0.543			
Hystologic type						
Squamous			Reference			
Adenocarcinoma	0.913	0.306-2.72	0.871			
Menopausal status						
Premenopause			Reference			
Postmenopause	0.845	0.323-2.208	0.731			
Tumor diameter						
≤ 2 cm			Reference			
> 2 cm	1.024	0.255-4.116	0.973			
FIGO Stage						
I			Reference			
II	1.463	0.461-4.638	0.518	1.433	0.428-4.799	0.559
III	4.117	1.577-10.752	0.004	5.233	1.469-18.639	0.01
IV	-	-	-			
Parametrial involvement						
No			Reference			
Yes	4.543	1.313-15.715	0.017	1.751	0.383-8.01	0.47
Depth of invasion						
<%50			Reference			
≥%50	0.001	0.001-0.001	0.981			
Full thickness invasion	0.541	0.0072-4.041	0.549			
LVSI						
No			Reference			
Yes	1.33	0.486-3.635	0.579			
Vaginal Involvement						
No			Reference			
Yes	1.526	0.188-12.422	0.693			
Perineural invasion						
No			Reference			
Yes	2.655	0.78-9.035	0.04	1.107	0.26-4.707	0.89
Pelvic lymph node involvement						
No			Reference			
Yes	2.494	0.911-6.827	0.05	1.687	0.041-1.182	0.01
Paraaortic lymph node involvement						
No			Reference			
Yes	6.784	1.502-30.653	0.013	3.793	0.534-26.945	0.183
Surgery						
Type 1 Hysterectomy			Reference			
Type 2 Hysterectomy	4.054	0.542-30.308	0.173			
Type 3 Hysterectomy	1.911	0.172-21.21	0.598			
Adjuvan Terapy						
Only surgery			Reference			
ERT	7.557	2.132-26.781	0.002	6.689	1.174-27.215	0.006
ERT+Brachiaterapy	9.216	1.925-44.128	0.005	10.477	1.848-59.405	0.008

DFS: disease free survival, HR: hazard ratio, CI: confidence interval ERT: External radiotherapy, LVSI: lymphovascular space invasion, FIGO: International Federation of Gynecology and Obstetrics

As a result of the cox regression analysis performed to determine the factors affecting DFS and OS, lymph node involvement and FIGO stage were found to be risk factors affecting OS and DFS. Variables that were found to be effective in univariate analysis were included in multivariate analysis. Accordingly, when the effect of other variables was controlled, lymph node involvement and FIGO stage were found to be important prognostic factors in determining OS and DFS. It was found that the risk of death is 3.13 times higher when there is pelvic lymph node involvement, and 13.16 times higher when there is paraaortic lymph node involvement. (**Table 3** and **Table 4**).

DISCUSSION

Cervical cancer is gaining more importance day by day due to its increasing incidence among patients. Generally, these patients are treated with radical hysterectomy and pelvic lymphadenectomy. However, very different prognoses are observed in patients at the same FIGO stage. Therefore, it is important to determine the prognostic factors affecting the survival rate in these cases. Few studies focus on overall trends in survival rates and discuss long-term observation of these patients.

The life expectancy of patients after radical hysterectomy and pelvic lymphadenectomy in cervical cancer depends on many factors. Treatment-related factors as well as the stage of cervical cancer are important prognostic factors (10). As the stage progresses, the response to treatment decreases. According to SEER data, 5-year survival after treatment in stage 1 cervical cancer is around 91.8%, while the same rate is around 15% in stage 4 cancer (6). Consistent with the literature, in our study, stage was the most significant predictor of both DFS and OS. According to the results of the presented study, 10-year OS after treatment in cervical cancer is 83.6%, 76.6% and 15.2% in Stage 1, stage 2, and stage 3 respectively. In addition, the probability of regional lymphatic metastasis increases as the stage progresses. This negatively affects the prognosis in cervical cancer. In many studies, it has been stated that lymph node involvement reduces survival statistically significantly (11). In a Japanese study involving 117 patients, patients were divided into two groups according to lymph node involvement, and 5-year survival was found to be 52% in the group with lymph node involvement and 89% in the group without lymph node involvement (p value=0.0005) (12). Presence of lymph node involvement is accepted as an independent risk factor for cervical cancer prognosis in the literature (13). In the study of Monaghan et al. (14) published in 1990 covering 498 cases, they found 5-year survival as 91% in lymph node-negative cases and 51% in cases with positive lymph node involvement. In a study by Kim et al. (15) published in 2000, involving 366 patients, 5-year survival was found to be 95% in lymph node-negative cases and 78% in cases with positive lymph node involvement. Similar results were found in this study, which supports the literature. Survival is reduced in patients with pelvic lymph node involvement. While the 10-year OS rate was 76.4% in patients with negative pelvic lymph nodes, this rate was 33.3% in patients with positive pelvic lymph nodes. Therefore, we believe that extraperitoneal lymph node sampling before surgery in cervical cancers will be beneficial.

In a study by Shinohara et al. (16) parametrial invasion, venous infiltration, pelvic lymph node metastasis, residual muscle layer thickness (<5 mm), tumor depth (≥13 mm) and invasive tumor growth pattern was examined as prognostic factors and shorter survival were found in patients with any of these factors in early stage cervical cancer patients who underwent radical hysterectomy and radiotherapy. In the study conducted by Burghardt et al. (17) which examined 1,004 cases covering 3 centers, 5-year survival was found to be 62.4% in cases with parametrial involvement, and this rate was 85.8% in cases without parametrial involvement. The results of this study were close to the literature in terms of parametrial involvement. Although parametrial involvement increased the risk of death 2.97 times in this study, it was not statistically significant (p=0.21). In the present study, consistent with the literature, lymph node involvement were found to be independent prognostic factors for both DFS and OS in multivariate analyzes. The most predictive parameters for PFS and OS were pelvic and paraaortic lymph nodes involvement, respectively.

Literature studies have stated that adenocarcinoma histological type is a poor prognostic factor by many centers (15,18). Many studies found no difference in survival by histologic subtype, but in the SEER database, which included 24562 cervical cancer patients, adenocarcinomas were reported to have shorter survival than same-stage squamous carcinomas (39% and 21% higher risk of death for early and advanced carcinomas, respectively) (18,19). In the study of the American Society of Surgeons, which included 157 cases treated between 1984 and 1990, 9,351 (83.8%) squamous cell cervical cancer, 1,405 (12.6%) adenocarcinoma and 401 adenosquamous cell cervical cancer were examined. No effect of histological type on overall survival could be demonstrated in clinically staged 1B cases (13). In our study, the histological subtype rates were consistent with the literature and our findings supported the SEER database. In this study, the 10-year survival rate for squmaous cell cancers was 59.9%, while it was 43.8 for adenocancers.

In a study conducted in our country, examining a total of 70 cases diagnosed with stage 1B2 and 2A2 cervical cancer, comparing radical hysterectomy+adjuvant chemoradiotherapy, primary chemoradiotherapy, neoadjuvant chemotherapy followed by radical hysterectomy, neoadjuvant chemoradiotherapy followed by radical hysterectomy, there was no statistically significant difference in OS and DFS between these 4 different treatment modalities. In the present study, it was determined that radical hysterectomy followed by adjuvant radiotherapy did not differ statistically in terms of OS and DFS

The most important limitations of our study are its retrospective nature and the small number of patients. The development of surgical techniques and the fact that there are some changes in the methods used with the following years prevent our study from being homogeneous. However, since all patients are operated and followed up by the same team, it is thought that homogeneity is achieved in this regard. The most important strength of this study is that it includes long-term results. It would be beneficial to confirm our results with prospective, multicenter studies with a larger number of patients.

CONCLUSION

Although the number of cases is limited, pelvic and paraaortic lymph node involvement and FIGO stage were found to be the most important prognostic factor regardless of histological type in cervical cancers. Survival was found to be significantly lower in patients with lymph node involvement. Except for lymph node involvement and FIGO stage, no effect of other prognostic factors on survival was found.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval for the study was obtained from Ethics Committee of Selçuk University (Date: 21.04.2021, Meeting no: 2021/08, Decision no: 2021/214).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Evaluation of neutrophyl/lymphocyte ratio, platelet/ lymphocyte ratio and mean platelet volume according to the disease activity index in patients of ankylosing spondylitis

Murat Doğan[1], Mehmet Zafer Boyacıoğlu[2], Ayşe Gülşen Doğan[2]

[1]Hitit University Erol Olçok Training and Research Hospital, Department Of Internal Medicine, Çorum, Turkey
[2]Hitit University Erol Olçok Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Çorum, Turkey

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ABSTRACT

Objective: To determine the relationship between neutrophil/lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR) and mean platelet volume (MPV) with acute phase reactants in patients with ankylosing spondylitis (AS) and to show the usability of these parameters in the activation periods and follow-up of the disease.

Material and Method: The demographic data (age, gender) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 70 patients who had been followed regularly for at least 1 year and whose diagnosis of AS was definite were recorded. The control group consists of 70 people who do not have any disease. Among the laboratory parameters, neutrophil, platelet, lymphocyte count, C-reactive protein(CRP), erythrocyte sedimentation rate(ESR), NLR, PLR and MPV values were retrospectively checked and recorded.

Results: In our study, a statistically significant difference was found between the AS patients and the control group in MPV, NLR and PLR values. In addition, these values were found to be statistically significantly different between the groups with low disease activity and high disease activity in the AS patient group. There was a weak negative correlation between MPV value and BASDAI, ESR and CRP values. There was no statistically significant correlation between NLR value and ESR and CRP. There was no correlation between PLR value and ESR and CRP.

Conclusion: As a result of our study, NLR, PLR and MPV values are seen as simple, easy and inexpensive markers that can be used to determine disease activity in AS patients.

Keywords: Ankylosing spondylitis, NLR, PLR

INTRODUCTION

Ankylosing spondylitis (AS) is the most common subtype of the Spondyloarthritis (SpA) group that causes inflammatory back pain. It is a common inflammatory disease that causes structural and functional disability (1). AS is an autoimmune disease which is manifested by a variety of genetic and environmental factors influence (2). Axial skeleton and especially sacroiliac joint involvement is prominent in AS (3). The most important complaint is inflammatory back pain. Enthesal and peripheral joint involvement is usually present. The most common extraarticular involvement is uveitis (4).

There is no specific laboratory finding to diagnose patients with AS. Acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be normal in patients with AS, but are frequently used in the diagnosis and treatment of the disease. Rheumatoid factor (RF) and antinuclear antibodies (ANA) are negative (5). Imaging methods are important in the diagnosis and classification of AS (6).

Because AS progresses with periods of exacerbation and remission, some scales are used in disease activation and evaluation of response to treatment.; It evaluates disease-specific symptoms such as fatigue, spinal and peripheral joint pain, swelling, and morning stiffness.

It is evaluated on scores ranging from 0-10. An increase in the score indicates an increase in disease activity. It is a reliable and change-sensitive scale developed to evaluate disease activity and progression (7).

Corresponding Author: Murat Doğan, murat404040@hotmail.com
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Recently, it has been found that neutrophil, lymphocyte and platelet values, which are a part of the immune system and obtained from the routine complete blood count in the follow-up of rheumatological diseases, are associated with autoimmune diseases, malignancies, inflammatory diseases and chronic diseases. In addition, it has been shown that neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are associated with ESR, CRP, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) values (8).

Mean platelet volume (MPV) is obtained directly from the hemogram parameter. It decreases in the activation of rheumatological diseases and shows a negative correlation with ESR, CRP. This may indicate that MPV can be used as a negative acute phase reactant. There are differences in studies on NLR and PLR in rheumatological patients.

The aim of our study is to determine the relationship between NLR, PLR, MPV values of our AS patients who are followed up in our outpatient clinic with acute phase reactants according to the disease activation level and to show the usability of these parameters during the activation periods and follow-up of the disease.

MATERIAL AND METHOD

This study was approved by the university/local human research ethics committee, and all procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards. Ethics committee approval was obtained from Hitit University Clinical Researchs Ethics Committee for the study (Date: 05.02.2020, Decision No: 169). In our study, the files of AS patients registered in Hitit University Erol Olçok Training and Research Hospital Physical Therapy and Rehabilitation Department between 2018-2019 were retrospectively scanned. Demographic data (age, gender) and BASDAI score of 70 patients who had been followed up regularly for at least 1 year and whose diagnosis of AS was definite were recorded. The control group consists of 70 people who do not have any disease. The exclusion criteria of the patient group were acute infection, diabetes, cancer or chronic diseases. Laboratory results of the patient and control groups were examined. CRP (mg/L), ESR (mm/h) values were obtained from biochemical analysis. Neutrophil (10^9/L), lymphocyte (10^9/L), platelet (10^9/L) counts and MPV (fL) values were obtained from the hemogram analysis. The NLR value was determined by dividing the neutrophil count by the lymphocyte count and the PLR value by dividing the platelet count by the lymphocyte count. Clinical evaluation and laboratory data of only one examination data of a patient were included in the study. The patient group was divided into two groups with BASDAI score below 4 as low activity and 4 and above high activity. CRP, ESR, platelet, MPV, NLR and PLR values obtained from routine hemogram analysis were compared with the disease and control groups. In addition, these values were compared in the patient group according to the BASDAI score.

Statistical Analysis

Statistical analyzes were performed using a package program called SPSS (IBM SPSS Statistics 24). Frequency tables and descriptive statistics were used in the interpretation of the findings. Parametric methods were used for measurement values suitable for normal distribution. In accordance with parametric methods, "IndependentSample-t" test (t-table value) method was used to compare the measurement values of two independent groups. Nonparametric methods were used for measurement values that are not suitable for normal distribution. In accordance with non-parametric methods, "Mann-Whitney U" test (Z-table value) method was used to compare the measurement values of two independent groups. The expected Pearson-$\chi 2$ and continuity correction cross tables were used to examine the relationships between two qualitative variables. "Pearson" correlation coefficient in examining the relationship of two quantitative data with normal distribution; "Spearman" correlation coefficient was used to examine the relationship of two quantitative data that do not have normal distribution. Binary Logistic Regression: Backward LR model was used to determine the factors affecting high disease activity.

RESULTS

There is no statistically significant relationship between the groups and gender ($p>0.05$). Groups are gender-neutral and homogeneous. A statistically significant relationship was found between the BASDAI classes of the patients and their gender ($\chi 2=6.121$; $p=0.013$). It was found that 23 (82.1%) of the women were in the low disease activity class and 21 (50.0%) of the men were in the high disease activity class. It was determined that those with low disease activity level were predominantly female, and those with high disease activity level were predominantly male (**Table 1**).

Table 1. Comparison of gender and groups

Variable \ Gender	Female		Male		Statistical analysis* Possibility
	n	%	n	%	
Group					
Ankylosing spondylitis	28	50.0	42	50.0	$\chi 2=0.000$
Control	28	50.0	42	50.0	$p=1.000$
Patient BASDAI class					
Low activity (<4)	23	82.1	21	50.0	$\chi 2=6.121$
High activity (≥4)	5	17.9	21	50.0	$p=0.013$

* Continuity correction or "Pearson-$\chi 2$" cross tables were used to examine the relationships of two qualitative variables.

A statistically significant difference was found between the groups in terms of CRP, MPV, NLR, Platelet and PLR values (p<0.05). The CRP, NLR, Platelet and PLR values of those in the ankylosing spondylitis group were found to be statistically significantly higher than those in the control group, and the MPV value was significantly lower (**Table 2**).

Table 2. Comparison of parameters according to groups

Variable / Group	Ankylosing spondylitis (n=70)	Control (n=70)	p value
	X⁻±SS	X⁻±SS	
Age (years)	41.08±10.25	42.54±10.45	0.052
Disease Duration (years)	6.25±2.4	-	
CRP(mg/L)	10.74±14.22	4.60±3.37	0.020
ESR (mm/h)	14.95±13.87	12.70±10.14	0.622
Neutrophil (10⁹/L)	4.33±1.35	4.07±1.30	0.245
Lymphocyte (10⁹/L)	2.29±0.79	2.46±0.64	0.055
NLR	2.06±0.89	1.75±0.71	0.010
Platelet(10⁹/L)	272.07±64.60	250.71±60.92	0.022
MPV(fL)	9.75±1.35	10.47±0.93	0.004
PLR	132.40±55.05	110.21±51.27	0.010

* IndependentSample-t test was used for comparing the measurement values of two independent groups in the data with normal distribution, and the "Mann-Whitney U" test statistics were used to compare the measurement values of two independent groups in the data without normal distribution.

While there was no statistically significant difference in age according to the BASDAI classes of the patients (p>0.05), a statistically significant difference was found in terms of CRP, ESR, platelet, NLR, MPV, PLR values (p<0.05). CRP, ESR, platelet, NLR, and PLR values of those in the high disease activity group were significantly higher, while MPV was significantly higher in the low disease activity group (**Table 3**).

There was a positive correlation between BASDAI score and CRP, ESR and a weak negative correlation with MPV. There was a weak correlation between CRP values and ESR in the positive direction and a negative correlation with MPV. In the correlation analysis of ESR values, negative weak correlation with MPV was obtained.

Table 3. Comparison of parameters in the patient group according to BASDAI classes.

Variable / BASDAI class	Low disease [<4] (n=44)	High disease [≥4] (n=26)	Statistical analysis
	X—±SS	X—±SS	
Age(years)	40.80±10.55	41.58±9.90	t=-0.306 p=0.760
CRP	4.42±2.90	21.43±18.82	p=0.000
ESR	11.41±9.59	20.92±17.72	p=0.018
NLR	1.95±0.84	2.26±0.94	p=0.047
Platelet	276.05±55.40	365.35±78.52	P <0.001
MPV	10.24±0.88	9.90±1.92	p=0.003
PLR	131.76±53.69	133.46±58.35	p=0.008

"Independent Sample-t" test (t-table value) for comparing the measurement values of two independent groups in the data with normal distribution; "Mann-Whitney U" test statistics were used to compare the measurement values of two independent groups in the data that did not have a normal distribution.

There was a weak positive correlation between NLR and PLR value, and a weak negative correlation between MPV and its value (**Table 4**).

Table 4. Correlation evaluations of some parameters of the patients

Correlation* (n=70) Variable		BASDAI score	CRP	ESR	NLR	PLR	MPV
BASDAI score	r	1.000	0.705	0.298	0.195	0.238	-0.305
	p	-	0.000	0.012	0.006	0.034	0.020
CRP	r		1.000	0.467	0.225	0.068	-0.285
	p		-	0.000	0.061	0.577	0.033
ESR	r			1.000	0.160	0.226	-0.301
	p			-	0.184	0.060	0.023
NLR	r				1.000	0.421	-0.299
	p				-	0.000	0.049
PLR	r					1.000	-0.044
	p					-	0.113

"Pearson" correlation coefficient was used to examine the relationship of two quantitative data with normal distribution, and "Spearman" correlation coefficient was used to examine the relationship of two quantitative data with no normal distribution.

DISCUSSION

Ankylosing spondylitis (AS) is a common rheumatic disease that predominantly affects the axial skeleton, with structural and functional disability causing inflammatory low back pain. More than 80% of patients usually start to show their first symptoms before the age of 30. Men are significantly more affected by the disease than women. In our study, a statistically significant relationship was found between BASDAI classes and gender. It was determined that those with low disease activity level were predominantly female, and those with high disease activity level were predominantly male.

MPV shows the average circulating platelet size obtained from a complete blood count. Its normal value is 7.5-11.5 fl. It is a parameter indicative of platelet function and activity, and it decreases with the pressure of pro-inflammatory cytokines and acute phase markers on the bone marrow in inflammation and shows a negative correlation in the inflammatory process (9,10). In studies conducted with RA patients, MPV levels were found to be lower in the patient group compared to the control group, and an inverse correlation was found with disease activity scores (11).

Negative correlations were found with BASDAI in AS patients, with CRP in psoriatic arthritis patients, and with ESR in SLE patients (12,13). Although many studies have suggested that MPV decreases in inflammatory diseases and it can be studied as a negative marker, some studies have found that MPV value is similar between AS patients and the control group and does not correlate with CRP (14). In our study, a statistically significant difference was found in MPV value between AS patients and the control group. MPV level was found to be significantly lower in AS patients. In addition, MPV value was found

to be statistically significantly higher in AS patients, in the group with low disease activity. There was a weak negative correlation between MPV value and BASDAI, ESR and CRP values.

It suggested that the increase in the number of neutrophils and platelets in the systemic circulation in the presence of inflammation, and the decrease in the number of lymphocytes, NLR and PLR parameters can be used as a marker in rheumatic diseases and in the activation periods of these diseases. The NLR value is an easy, cheap and simple parameter obtained by dividing the number of neutrophils obtained from the complete blood count by the number of lymphocytes and the PLR value by the number of lymphocytes (15). In recent studies, there are many studies showing the usability of NLR and PLR as inflammatory and activity markers in inflammatory rheumatic diseases. In some studies, it was reported that the NLR value was higher in the active disease group than in the inactive disease group according to the BASDAI score and there was a positive correlation between the BASDAI score and the NLR value. Contrary to these studies, there are also studies that could not find a correlation between BASDAI and NLR (10,16,17). It is included in studies in which a significant positive correlation was found between NLR values and ESR and CRP levels (17). In our study, the NLR values were found to be statistically significantly different between the AS patients and the control group, and the AS group with high disease index and the AS group with low disease index. In our study, no statistically significant correlation was observed between NLR value and ESR and CRP.

PLR has been found as an inflammatory marker and a valuable prognostic factor in some malignancies and patients diagnosed with heart failure (17,18). In a study conducted with AS patients, a significant statistical difference was found between the patient group and the control group in PLR value (17). In a meta-analysis study, PLR values did not differ significantly between the patient and control groups (14). In some correlation studies, a positive correlation was found between PLR and ESR and CRP (16,19). In our study, the PLR value was found to be statistically significantly different in both the patient group and patients with AS with high activity index. There was no correlation between PLR value and ESR and CRP.

CONCLUSION

As a result of our study, NLR, PLR and MPV values are seen as simple, easy and inexpensive markers that can be used to determine disease activity in AS patients. The limitation of our study is that it is retrospective. These parameters may also guide new indices to be investigated in future studies for AS diseases, and we believe that they will contribute to the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Hitit University Clinical Researchs Ethics Committee (Date: 05.02.2020, Decision No: 169).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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An investigation of the efficiency of pedicle screw simulator software in thoracic

İlker Deniz Cingöz[1], Gökhan Gürkan[2], İsmail Kaya[1], Murat Atar[3], İnan Uzunoğlu[4], Meryem Cansu Şahin[5], Nurullah Yüceer[2]

[1]Usak University, Faculty of Medicine, Department of Neurosurgery, Uşak, Turkey
[2]Katip Çelebi University, School of Medicine, Department of Neurosurgery, İzmir, Turkey
[3]Sultan 2. Abdulhamid Han Training and Research Hospital, Department of Neurosurgery, İstanbul, Turkey
[4]University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Neurosurgery, Ankara, Turkey
[5]Kutahya Health Sciences University, Research and Training Center, Kütahya, Turkey

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ABSTRACT

Aim: Fennell et al. describe a simple, effective freehand technique for thoracic pedicle screw insertion. In this study, we aimed to compare the patients undergoing upper thoracic pedicle screw insertion with the Fennell technique simulated on Pedicle Screw Simulator (PSS) and those recruited to the same procedure utilizing C-arm fluoroscopy.

Material and Method: First, we uploaded pre-operative CT images of 12 patients to the PSS module, which was used in our study to calculate the screw angle and visualize the pedicle screw entry point and trajectories. Then, we created three-dimensional vertebral models of the patients to simulate screw placement using visualization tool kit (VTK), open-source software for 3D computer graphics and visualization, available free of charge as part of 3D Slicer. Next, we placed pedicle screws through pre-determined anatomic regions. C-arm fluoroscopy-guided pedicle screws were placed in the patients in the control group. The amount of bleeding, operation times and correct screw placement data were recorded in both groups.

Results: 24 patients were included in the study. The mean age of the patients was 32.3±4.1 years. We applied 80 pedicle screws to Group 1 and 72 to Group 2. According to the malposition classification by Rao et al. on postoperative CTs, 68 patients in Group 1 were classified as Grade 0, 8 as Grade 1, 4 as Grade 2. Yet, there were no statistical differences between the groups by Rao et al.'s classification ($p>0.05$). While the mean operation time of Group 1 was 138±34 minutes, it was 162±44 minutes in Group 2. The groups significantly differed by operation time ($p<0.05$).

Conclusion: Overall, pre-operative simulation on PSS may allow more efficient and easier thoracic pedicle screw application. In addition, the simulator may contribute to the training of surgeons on upper thoracic pedicle screw application and increase the accuracy of pedicular screw placement.

Keywords: Freehand technique, pedicle screw simulator, upper thoracic pedicle screws

INTRODUCTION

Incorrect placement of pedicle screws can lead to serious complications (1-5). Pedicle screws can safely be inserted using intraoperative tools such as fluoroscopy and computed tomography-guided (CT) navigation (6). Yet, variations in vertebrae particularly make pedicle screw insertion difficult. Moreover, the use of navigation is not common in our country due to its high cost. In addition, surgeons have serious concerns about radiation exposure when using fluoroscopy.

Today, pre-operative simulation software serves to verify the reliability of various techniques in screw placement and is used in the training of spine surgeons (7-9). Accordingly, Pedicle Screw Simulator (PSS) is a versatile module that can be used for pre-surgical planning in 3D Slicer, an open-source platform developed for this purpose (10,11).

Placement of an upper thoracic pedicle screw with fluoroscopy, but without a pre-operative navigation system, is also challenging for surgeons. It also requires a large number of fluoroscopy shots. To overcome this situation, Fennell et al. describe a simple, effective freehand technique of thoracic pedicle screw insertion using a uniform entry point for all levels (12).

Corresponding Author: İlker Deniz Cingöz, i.d.cingoz@hotmail.com
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Ultimately, this study aimed to compare the patients undergoing upper thoracic pedicle screw insertion with the Fennell technique simulated on pedicle screw simulator (PSS) and those recruited to the same procedure utilizing C-arm fluoroscopy.

MATERIAL AND METHOD

The study was carried out with the permission of Uşak University Non-Interventional Clinical Research Ethics Committee (Date: 23.09.2021, Decision No: 175-175-09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We recruited 24 patients for whom a surgical treatment (pedicle screw) was planned for a pathological fracture (non-traumatic) in the upper thoracic region (T1-T6 vertebrae). We applied pedicle screwing on 12 patients (Group 1) with the Fennell technique simulated on PSS, while the procedure was performed on 12 patients in the control group (Group 2) with the help of C-arm fluoroscopy.

Patients who underwent posterior transpedicular screw for upper thorax pathological fracture and gave informed consent were included in the study. Patients with a history of trauma and thoracic spine surgery were excluded from the study.

Pre-operative Planning

In our study, we utilized PSS (http://www.slicer.org, Surgical Planning Lab (SPL), Boston, USA) module on the 3D Slicer environment coded in Python language. We reconstructed CT data with a slice thickness of 1 mm, a spacing of 1 mm between axial slices, and a matrix size of 512 × 512 for each slice.

We uploaded pre-operative CT images of Group 1 to the PSS module, which was used in our study to calculate the screw angle and visualize the pedicle screw entry point and trajectories. This method allowed the surgeon to finalize pre-operative planning in a short time. Then, we created three-dimensional vertebral models for the patients to simulate screw placement using VTK (Visualization Tool Kit), open-source software for 3D computer graphics and visualization, available free of charge as part of 3D Slicer (**Figure 1**).

Next, we set two trajectory planning modes using the respective vertebrae, with ET (Entry-Target mode) and EA (Entry-Angle mode) on the control panel. We then selected the desired vertebral level using the plus sign on the 3D Slicer toolbar (**Figure 2**).

In ET mode, we selected the entry and target reference points for the pedicle screw through axial, sagittal, and coronal CT series and the 3D vertebra model. Then, we calculated the pitch and deviation angles for the desired pedicle screw using the software and selected desired diameter of the pedicle screw on the PSS control panel. Afterward, we visualized the trajectory of the pedicle screw using the "place screw for given entry and target" button. The length of the screw was calculated on the program based on the Euclidean distance between the desired entry and target reference points (**Figure 3**).

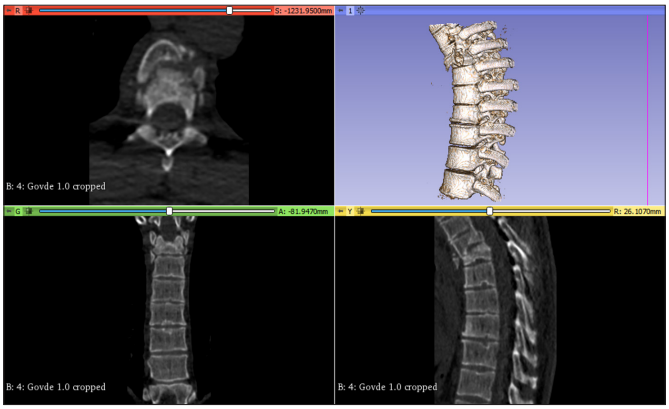

Figure 1. 3D vertebra model on preoperative CT images extracted using Visualization Tool Kit

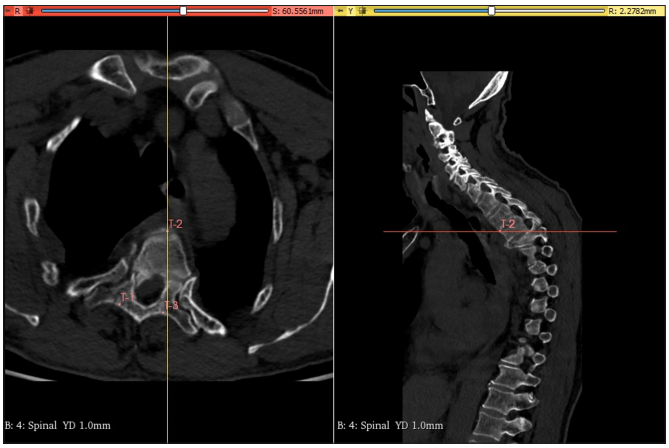

Figure 2. Selecting the desired vertebral level in 3D Slicer

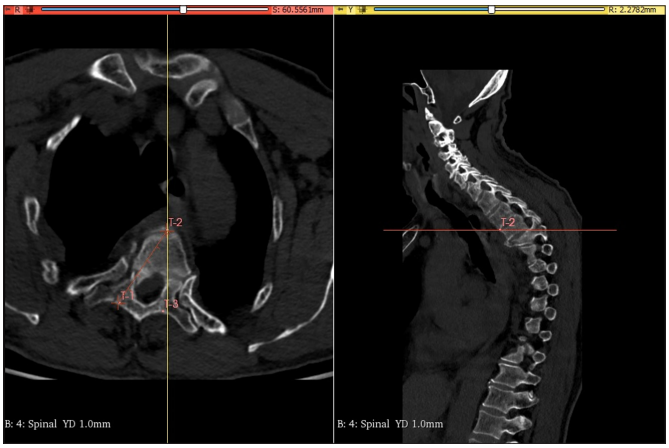

Figure 2. Calculation of Euclidean distance between reference points

On the other hand, in EA mode, the appropriate entry and reference points were selected on the panels through axial, sagittal, and coronal series and 3D vertebra models. Then, we entered the desired slope, deviation angle, length, and diameter values of the pedicle screw into the PSS control panel. The "insert the screw for given angle" tab button was activated to visualize the desired pedicle screw (**Figure 4**).

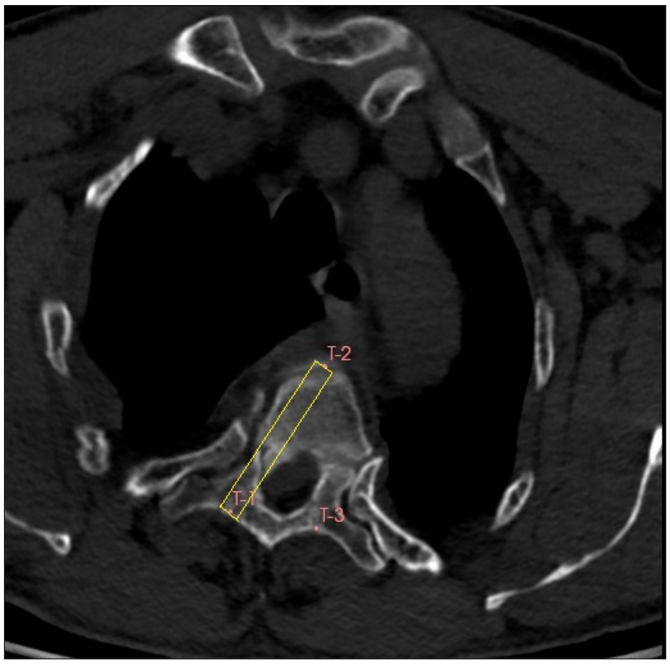

Figure 4. Visualization of the desired pedicle screw

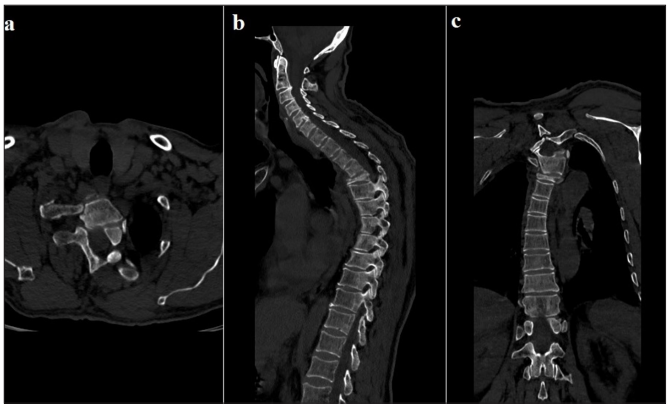

Figure 5. Preoperative CT images

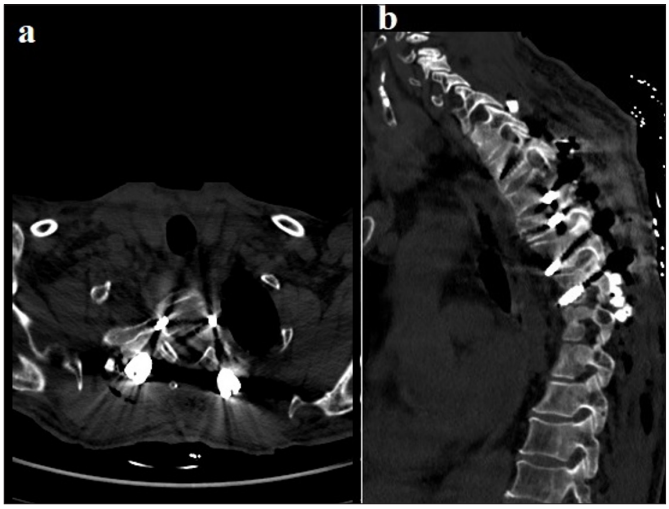

Figure 6. Postoperative CT images

Operational Methods

We placed pedicle screws through pre-determined anatomic regions. In the other group, pedicle screws were placed under fluoroscopic control.

Evaluation

The amount of intraoperative bleeding, operation times and screw placement success of the patients were recorded. We then performed control CT scans after the operations (**Figure 5**, **6**). We recorded screw malpositions evaluated them using Rao et al.'s classification (13). The grading scale is evaluated as follows: 0=no perforation of the pedicle; 1=< 2 mm pedicle perforation with one screw thread out of the pedicle; 2=2-4 mm pedicle perforation; 3=> 4 mm pedicle perforation.

Statistical Analysis

We analyzed the data using the SPSS (version 20, IBM Inc., Armonk, USA) program. Quantitative data were presented as means and standard deviations, while qualitative data were given as percentages. We performed Chi-square to compare the categorical variables. we considered a p-value of < 0.05 statistically significant.

RESULTS

We studied 24 patients (mean age=32.3±4.1 years, 14 (58.3%) were male, preoperative PSS was performed in 12 (50%) patients. There were no statistically significant differences between the groups by age and gender (p>0.05) (**Table 1**). We applied 80 pedicle screws to Group 1 and 72 to Group 2. According to the malposition classification by Rao et al. on postoperative CTs, 68 patients in Group 1 were classified as Grade 0, 8 as Grade 1, 4 as Grade 2. When it comes to the control group (Group 2), 61 patients were classified as Grade 0, 6 as Grade 1, 4 as Grade 2, and 1 as Grade 3. Yet, there were no statistical differences between the groups by Rao classification (p>0.05) (**Table 2**).

Table 1. Demographic information of the groups

	Group 1	Group 2	p-value †
Number of patients	12	12	-
Sex	8 males/4 females	6 males/6 females	0.234
Age	35.3±4.3	29.3±3.9	0.196

Table 2. Rao et al.'s malposition classification on postoperative CTs		
	Group 1 (n=80 screws)	Group 2 (n=72 screws)
Grade 0 (completely within the pedicle)	68	61
Grade 1 (perforation <2 mm)	8	6
Grade 2 (perforation between 2–4 mm)	4	4
Grade 3 (perforation >4 mm)	-	1
Accuracy †	95%	93.1%
† Accuracy = (Grade 0 + Grade 1)/n * %100		

While the mean operation time of Group 1 was 138±34 minutes, it was 162±44 minutes in Group 2. The groups significantly differed by operation time (p<0.05) (**Table 3**). Mean blood loss amounts were 662±92 mL in Group 1 and 732±88 mL in Group 2 (p>0.05) (**Table 3**).

Table 3. Surgical data			
	Group 1 (n=12)	Group 2 (n=12)	p value †
Operation time (min)	138±34	162±44	p<0.05
Blood loss (mL)	662±92	732±88	p>0.05

DISCUSSION

The developments in spine surgery have contributed to the common use of the posterior thoracic interpedicular screwing method today. Due to the complexity of the anatomy of the thoracic pedicles, screw placement is difficult, especially in thoracic fractures. Thoracic pedicles are thin, short, narrow and fragile, causing easy fracture of thoracic pedicles during screwing (14).

Malposition rates can reach 30-40% in thoracic pedicle screw placement (15). In general, pedicle screw placement is assisted with intraoperative aids such as C-arm fluoroscopy and computed tomography-guided (CT) navigation (6). Besides, CT-guided navigation is costly, so not widely adopted in our country (16). Instead, pedicle screws are commonly placed with the help of C-arm fluoroscopy. However, intraoperative fluoroscopy in long-level fusion surgeries leads surgeons and patients to be exposed to radiation for a longer time (17), which creates a significant problem.

3D Slicer is free and visualization software. This program has an extension called pedicle screw simulator (PSS), which is used in spinal surgery planning. The software allowed us to determine the entry point, direction, diameter, and length of pedicle screws under the guidance of the Fennell technique before spinal surgery; we effectively simulated the Fennell technique on PSS.

In their study, Swaminathan et al. (18) simulated the placement of 120 thoracic pedicle screws on the pre-operative PSS. They reported that the simulation allowed successful screw placement both in the craniocaudal and medial-lateral directions. In our study, we concluded that PSS was useful for surgeons, especially for understanding the craniocaudal angle when placing pedicle screws.

In the literature, there were high malposition rates in upper thoracic interpedicular screwing applied through C-arm fluoroscopy (19,20). Karagöz et al. (19) a study of 24 patients retrospectively analyzed 113 thoracic pedicle screws. As a result, they found the rate of incorrect pedicle screw placement to be 20.3%. Also, Vaccaro et al. found the rate of incorrect screw placement to be 41% on postoperative CT scans (20). In our study, the malposition rates in both the patient group (15%) and the control group (15.3%) were lower than those in the literature. In our study, there was no significant difference between the groups in terms of malposition rate (p>0.05).

The relevant literature proposes that the use of pre-operative simulation reduces the surgeon's margin of error and operation time (16). In our study, we found that operation time was significantly shorter in the patient group (p<0.05). Although the amount of bleeding was less in the patient group, the difference was not statistically significant (p>0.05). Further large-scale research may obtain significant results on bleeding amount and surgery duration.

It is known that complications occur in inserting pedicle screws, especially in the early learning period (21). In this context, the greatest advantage of such simulators may be that they allow novice surgeons and medical students to make effective pre-operative plans.

This study inevitably bears limitation. The sample size remained relatively small in this study. Hence, large-scale studies may be needed to conclude more robust results.

CONCLUSION

Overall, we concluded that pre-operative simulation on PSS may allow more efficient and easier thoracic pedicle screw application. In addition, the simulator may contribute to the training of surgeons on upper thoracic pedicle screw application and increase the accuracy of pedicular screw placement. The present study may guide further studies with diverse samples and simulators with more advanced technology.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Usak University Non-Interventional Clinical Researchs Ethics Committee (Date: 23.09.2021, Decision No: 175-175-09).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Comparison of visual and refractive outcomes between femtosecond laser-assisted in situ keratomileusis (FS-LASIK) and photorefractive keratectomy (PRK): a long-term outcomes analysis

Mehmet Fatih Karadağ

Dünyagöz Hospital, Department of Ophthalmology, Gaziantep, Turkey

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ABSTRACT

Aim: We aimed to compare the results of photorefractive keratectomy (PRK) and femtosecond-assisted laser in situ keratomileusis (FS-LASIK) procedures in the treatment of myopia and myopic astigmatism.

Material and Method: Seventy eyes of 35 patients with myopia and/or myopic astigmatism who had undergone PRK procedure were compared retrospectively with 70 eyes of 35 patients with myopia and/or myopic astigmatism who had undergone FS-LASIK procedure.

Results: All patients completed the 2-year follow-up period. With respect to age and sex, PRK and FS-LASIK groups were comparable. The differences in uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and spherical equivalent were significantly better with PRK than with FS-LASIK at 6- and 24-month visits. FS-LASIK and PRK had similar values of safety index, efficacy index, and predictability at 6 and 24 months postoperatively. No significant complications were observed in neither of the procedures during the follow-up period.

Conclusion: Both PRK and FS-LASIK seem equally effective options for the correction of myopia and myopic astigmatism. However, PRK provided slightly better visual and refractive outcomes than FS-LASIK at 6 and 24 months postoperatively.

Keywords: Laser in situ keratomileusis, myopia, myopic astigmatism, photorefractive keratectomy, refractive surgery

INTRODUCTION

Two frequently utilized types of refractive surgery, one of the most frequently performed elective procedures in ophthalmic surgery practice, are photorefractive keratectomy (PRK) and laser-assisted in situ keratomileusis (LASIK). On the one hand, PRK is a surface ablation procedure in which the epithelial layer of the cornea is removed, followed by laser ablation applied to the corneal stroma to change the refractive power (1). On the other, femtosecond laser-assisted LASIK (FS-LASIK) uses infrared light (1,053 nm) to produce microplasma and microcavitation bubbles within the corneal stroma and thereby functionally create a corneal dissection plane interface that can be manually opened with minimal effort (2).

Since its introduction in 2001, femtosecond laser technology has continued to evolve and even become the preferred method for flap creation in most LASIK operations (3). The rapid improvement in vision and lack of postoperative pain with LASIK has also made it preferred by patients over PRK, which causes greater postoperative discomfort and prolongs the recovery of visual acuity (4). On the other hand, PRK eliminates flap-related complications and may be associated with a decreased incidence of postoperative dry eye. Beyond that, in response to PRK's major complications—corneal haze and regression in patients with high-diopter (D)—use of mitomycin-C (MMC) was devised to decrease the development of major complications (5). Studies have also shown favorable visual and refractive outcomes with PRK–MMC used to treat cases of high myopia in the short- and long-term (6,7).

Although many studies have evaluated the efficacy and safety of FS-LASIK and PRK in isolation (8), to our knowledge, few studies compared the long-term results

Corresponding Author: Mehmet Fatih Karadağ, drmfkaradag@gmail.com
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of patients who underwent either PRK or FS-LASIK (9, 10). Thus, the aim of the present study was to compare visual and refractive outcomes in patients 24 months after they received PRK or FS-LASIK to treat myopia or myopic astigmatism.

MATERIAL AND METHOD

The study protocol was approved by Dünyagöz Hospital Ethics Committee (Date: 16.09.2021, Decision No: 2021/833). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

Eyes and the Setting

This retrospective, comparative study was performed by reviewing the charts of patients with varying severity of myopia and myopic astigmatism who underwent FS-LASIK or PRK at a private ophthalmology clinic in Turkey. All of the surgical procedures were performed by the same ophthalmic surgeon (MFK). To ensure equal conditions, operated eyes were selected in consecutive patients by turn. Exclusion criteria were as follows: the presence of concurring ocular or systemic disease, unstable refractive error, manifest or suspected corneal ectatic disorders, history of herpetic keratitis or corneal dystrophy, corneal scarring, cataract, glaucoma, pregnancy, and active use of isotretinoin or hormonal therapy. Contact lenses were discontinued 2 weeks prior to screening for soft contact lens wearers and 6 weeks prior to screening for rigid gas permeable lens wearers.

Pre- and Post-operative Assessments

All patients underwent a preoperative examination involving assessment of uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), intraocular pressure measurement, slit-lamp examination of the anterior segment, and dilated fundus examination at initial preoperative evaluation. All assessments were repeated postoperatively on day 1, at week 1 and at months 1, 3, 6, 12, and 24.

Visual acuity was recorded in both Snellen notation and logarithm of the minimum angle of resolution (logMAR) format. The efficacy index was defined as the ratio of postoperative UDVA to preoperative CDVA. The safety index was defined as the ratio of mean postoperative CDVA to mean preoperative CDVA. Predictability was presented as the percentage of eyes within±0.50 D postoperatively. They were calculated separately for the FS-LASIK and PRK groups.

Surgical Procedures

PRK was offered to patients whose central pachymetry was less than 500 μm (i.e., PRK Group), whereas FS-LASIK was offered to patients whose central pachymetry exceeded 500 μm (i.e., FS-LASIK Group). In using both techniques, a residual stromal bed thickness of more than 300 μm was preserved. The target refraction in all patients was emmetropia.

In the PRK group, the epithelial layer of the anesthetized (proparacaine hydrochloride 0.5%) cornea was removed mechanically. The VISX STAR S4 Excimer Laser (VISX Inc., Santa Clara, CA, USA) was used for corneal ablation, performed with a 1.25-mm blend zone and a 6.5-mm ablation zone. Following ablation, 0.02% MMC was applied to the stromal bed for 30 seconds to prevent scarring and haze, after which the bed was washed with a balanced salt solution to remove any debris. After irrigation with 30 mL of balanced salt solution, a bandage contact lens (Air Optix, CIBA VISION) was fitted over the treated cornea for 4 days. After the surgical procedure, each patient was prescribed a topical steroid (dexamethasone sodium phosphate 0.1%) 4 times daily for 3 weeks, a topical antibiotic (besifloxacin 0.6%) thrice daily for a week, nepafenac 0.1% thrice daily for 3 weeks, and preservative-free artificial tears (trehalose 3%, sodium hyaluronate 0.15%) 5 times daily for 3 months. Each patient was examined on a daily basis until the epithelium healed completely.

In the FS-LASIK group, following topical anesthesia, a 110-μm thick flap was attempted using the 150-kHz IntraLase iFS (Abbott Medical Optics, Santa Ana, CA, USA) femtosecond laser platform. After lifting the flap, corneal ablation was performed using the VISX STAR S4 Excimer Laser (VISX Inc., Santa Clara, CA, USA), with a 6.5-mm optical zone and 1.25-mm blend zone. Following irrigation with a balanced saline solution, the flap was repositioned. Postoperative treatment was the same as in the PRK group.

Statistical Analysis

All statistical analyses were performed using the SPSS statistical software version 25.0 (IBM, Armonk, NY, USA). For each variable, the normality of the data distribution was evaluated using the Kolmogorov–Smirnov test. The normality test showed that each numerical variable was normally distributed. All values were reported as the number (n) or mean±standard deviation. The categorical data were analyzed using the chi-square test. The Independent Samples t-test was used to compare the variables between the FS-LASIK and PRK groups. One-way analysis of variance (ANOVA) was used to analyze timely changes postoperatively, and Dunnett's test was used for multiple comparisons. A value of $p<0.05$ was defined for statistical significance.

RESULTS

The study included 140 eyes of 70 patients with myopia and/or myopic astigmatism, half of whom received FS-LASIK (n=70 eyes, Group 1), whereas the other half received PRK (n=70 eyes, Group 2), between September 2018 and September 2020. The demographic, as well as preoperative and intraoperative clinical characteristics of the patients, are summarized in **Table 1**. FS-LASIK group contained 17 men and 18 women with a mean age of 28.14±6.03 years, PRK group contained 18 men and 17 women with a mean age of 26.51±6.05 years. The distribution of patients by age and gender in the FS-LASIK group versus the PRK group did not differ significantly (P=.113 and P=.951, respectively). Furthermore, preoperative clinical parameters regarding central corneal thickness, spherical equivalent, astigmatism, average keratometric value, UDVA, and CDVA were similar between the groups.

All postoperative follow-up visits were completed in both groups. No severe complications were observed during the follow-up periods, such as corneal ectasia, epithelial ingrowth, diffuse lamellar keratitis, transient photosensitivity syndrome, severe dry eye, or keratitis.

The changes in average visual acuity and refraction parameters are summarized in **Table 2**. UDVA, CDVA, spherical equivalent, and cylindrical refraction values were successfully improved in both groups at the end of 24 months (p< 0.001, for all). The differences in UDVA, CDVA, and spherical equivalent were significantly slightly better in the PRK group than in FS-LASIK at 6- and 24-months follow-up. No statistically significant differences were observed in cylindrical refraction between the groups 6 and 24 months after surgery.

Table 3 shows the comparison of safety index, efficacy index, and predictability values between the groups. FS-LASIK and PRK have similar values of safety index, efficacy index, and predictability at 6 and 24 months postoperatively.

Table 1. The demographic and preoperative clinical characteristics

Parameters	WFG FS-LASIK	PRK	p values
Age (Years)	28.14±6.03	26.51±6.05	0.113[a]
Gender (male/female)	17/18	18/17	0.951[b]
CCT (μm)	534.12±31.42	539.25± 28.12	0.457[a]
SE (D)	-3.25±1.65	-3.18±1.72	0.256[a]
Astigmatism (D)	-0.84±0.75	-0.91±0.71	0.574[a]
K average (D)	43.74±1.51	43.53±1.42	0.321[a]
UDVA (LogMAR)	1.25±0.20	1.22±0.21	0.725[a]
CDVA (LogMAR)	-0.01±0.04	-0.01±0.05	0.856[a]

Abbreviations: D; diopter, CCT; central corneal thickness, SE; spherical equivalent, K; keratometry, UDVA; uncorrected distance visual acuity, CDVA; corrected distance visual acuity. Values are expressed as n or mean±standard deviation. a Independent sample test, b Chi-squared test.

Table 2. The preoperative and postoperative findings of patients

Groups	UDVA (logMAR)	CDVA (logMAR)	Spherical Equivalent (D)	Cylindrical Refraction (D)
WFG FS-LASIK (n=70)				
Preoperative	1.25±0.20	-0.01±0.04	-3.25±1.65	-0.84±0.75
6 months	0.01±0.07	- 0,03 ±0.04	-0.37±0.26	-0.31±0.33
24 months	-0.01±0.05	-0.06±0.03	-0.27±0.23	-0.09±0.21
p values a	< 0.001	< 0.001	< 0.001	< 0.001
PRK (n=70)				
Preoperative	1.22±0.21	-0.01±0.05	-3.18±1.72	-0.91±0.71
6 months	-0.04±0.07	-0.07±0.05	-0.21±0.34	-0.28±0.27
24 months	-0.08±0.06	-0.11±0.04	-0.11±0.23	-0.12±0.22
p values a	< 0.001	< 0.001	< 0.001	< 0.001
p values b between groups				
Preoperative	0.725	0.856	0.256	0.574
6 months	0.009	0.005	0.004	0.512
24 months	0.001	0.002	0.003	0.445

Abbreviations: D; diopter, UDVA; uncorrected distance visual acuity, CDVA; corrected distance visual acuity. Values are expressed as mean±standard deviation. a Repeated measured test, b Independent sample test

Table 3. Comparison of Safety Index, Efficacy Index, and Predictability values between the groups

	WFG FS-LASIK (n=70)	PRK (n=70)	p values[a]
Safety Index			
6 months	1.11±0.06	1.12±0.07	0.398
24 months	1.10±0.06	1.13±0.04	0.431
Efficacy Index			
6 months	1.08±0.11	1.09±0.12	0.312
24 months	1.07±0.11	1.08±0.10	0.362
Predictability (%)			
6 months	92.93	94.43	0.192
24 months	92.03	95.48	0.179

Abbreviations: PRK; Photorefractive keratectomy, WFG FS-LASIK; Wave Front-Guided Femtosecond LASIK Femtosecond laser in situ keratomileusis, a Independent sample test

DISCUSSION

The main findings of the present study were as follows: (i) Both PRK and FS-LASIK achieved the treatment goal, the visual outcomes of PRK were slightly better than FS-LASIK at 24 months, though. (ii) No intraoperative or postoperative complications arose in any of the study participants. (iii) Ours was among the studies with the longest follow-up duration in comparison of PRK vs. FS-LASIK.

Studies with long-term follow-up periods to compare PRK with flap-based procedures have been few and far between. Steinert et al. (11) who compared the outcomes of LASIK and PRK in patients with myopia, found similar efficacy indices between the groups at 12 months, although the improvement in UDVA was more rapid with LASIK than with PRK. Also, in that study, patients who underwent LASIK showed a tendency toward under-correction more than patients who underwent PRK (11).

Similarly, in a randomized clinical trial comparing PRK and LASIK, Hersh et al. (12) observed similar efficacy indices between the groups at 12 months, although patients who underwent LASIK again displayed a greater tendency toward under-correction than patients who underwent PRK.

By contrast, some studies have revealed slighter higher efficacy in eyes treated with PRK than with LASIK (13,14). Wallau and colleagues (15) compared LASIK and PRK with MMC and found that UDVA was significantly higher in patients who underwent PRK with MMC than in ones who underwent LASIK both at 3 and 6 months after surgery. In another clinical trial comparing PRK with mechanical epithelial removal, transepithelial PRK, laser-assisted subepithelial keratectomy (LASEK), and LASIK, visual outcomes at postoperative 12 months were slightly better in patients who underwent PRK with mechanical epithelial removal and transepithelial PRK than in their counterparts who underwent LASIK or LASEK (16). Aslanides et al. (17) additionally found that single-step modified transepithelial PRK and conventional alcohol-assisted PRK provided significantly better UDVA than LASIK for patients with myopia of 6.00 D or more at 12 months. In contrast to those studies, however, Van Gelder et al. (18) reported that in patients with mild to moderate myopia, flap-based surgeries provided better visual and more predictable refractive outcomes than PRK-based surgeries.

In line with the previous studies in the literature, we found slightly better UDVA, CDVA, and spherical equivalent values in patients who underwent PRK than in ones who underwent FS-LASIK at 6 months. Moreover, that difference remained statistically significant 24 months after the procedures, and the safety index, efficacy index, and predictability were all similar in both groups at 6 and 24 months postoperatively. Although other researchers found that the rate of reported complications developing in patients who underwent LASIK was higher than in ones who underwent PRK (16), we observed no complications in either group in our study. Therefore, we do not think that the difference in UDVA was due to a high rate of complications in FS-LASIK. In our opinion, the main reason for this may be due to the high-order aberrations triggered in patients who received FS-LASIK and structural changes caused by the creation of a corneal flap. Indeed, past studies have demonstrated that higher-order optical aberrations and systematic changes in corneal topography can be associated with uncomplicated lamellar flap creation (19, 20).

The major limitation of our retrospective evaluation was the lack of any assessment of contrast sensitivity, corneal aberrations, and other corneal biomechanics. The absence of those additional corneal tests limited our ability to determine the true cause of the difference in visual acuity with either surgical modality.

CONCLUSION

The present study is one of the few studies with the longest follow-up duration for postoperative outcomes. Our study revealed that PRK and FS-LASIK were equally effective procedures for correcting myopia and astigmatism. Though statistically insignificant, PRK provided slightly better visual and refractive outcomes than FS-LASIK at 6 and 24 months postoperatively..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Dünyagöz Hospital Ethics Committee (Date: 16.09.2021, Decision No: 2021/833).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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A comparison of idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonia in terms of anterior mediastinal fat properties

Sertan Bulut[1], Deniz Çelik[2], Hakan Ertürk[3], Harun Karamanlı[1], Mustafa Engin Şahin[1], Özlem Sönmez[1], Çiğdem Biber[1]

[1]University of Health Sciences, Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Pulmonology, Ankara, Turkey
[2]Alanya Alaaddin Keykubat University, Medical Faculty, Department of Pulmonology, Antalya Turkey
[3]University of Health Sciences Atatürk Chest Diseases and Thoracic Surgery Education and Research Hospital, Department of Radiology, Ankara, Turkey

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ABSTRACT

Aim: The shape and physical properties of the anterior mediastinum can be easily affected by inflammatory lung diseases, tuberculosis, empyema, radiotherapy, chronic fibrotic lung diseases, previous surgery, and after steroid therapy. We planned to compare the properties of anterior mediastinal fat (AMF) in 3 different groups: patients with idiopathic pulmonary fibrosis (IPF), patients with chronic hypersensitivity pneumonia (cHP), and in the healthy control group. We investigate the AMF shape, dimensions, and AMF area properties on the images of high-resolution computed tomography (HRCT) and to find any difference between IPF and cHP patients in terms of AMF.

Material and Method: The study comprises a total of 80 cases in the three groups. The first group comprises 26 cases diagnosed as IPF. The second group comprises 19 cases diagnosed as cHP. The third group comprises 35 control patients. The clinical, demographical, and AMF characteristics on HRCT were retrospectively evaluated. The AMF shape and area characteristics were compared between the three groups.

Results: There was no statistical difference between the mean ages of cases, BMIs, and smoking status in IPF, cHP, and control groups. Gender distribution was found statistically significant between the 3 groups (p=0.001). A statistically significant difference was observed between the IPF and cHP groups in terms of FVC levels (2.67±0.59, 2.14±0.80, respectively; p=0.024). Also, a statistically significant difference was observed between the IPF and cHP groups in terms of DLCO levels (57.42±17.21; 77.31±35.21; respectively; p=0.016). In the evaluation of AMF shape properties between two groups (cHP and IPF), the concave figure was significantly more frequent in cHP group (p=0.014). The AMF area analyses revealed that the IPF group's areas were significantly greater than the cHP and control group's. The AP dimension of AMF analyses revealed that only the cHP group's dimensions were significantly smaller than the control group's (p=0.037). In the analysis of the transverse dimension of AMF, the IPF group's dimensions were significantly greater than the cHP and control group's (p<0.0001 and p=0.007; respectively) and also the cHP group's dimensions were significantly greater than the control group's (p<0.0001).

Conclusion: The transverse length, total AMF area, and shape characteristics of AMF can be evaluated as a radiological marker for differential diagnosis of IPF and cHP, whose differential diagnosis may be difficult. Both the transverse length and AMF area can take greater values in the IPF group than in the cHP group.

Keywords: Idiopathic pulmonary fibrosis, chronic hypersensitivity pneumonia, anterior mediastinal fat

INTRODUCTION

Interstitial lung diseases (ILDs) are chronic lung diseases with similar clinical, radiological and pulmonary function test results (1). Although IPF is one of the most common forms of ILD, its origin is still uncertain and it has a poor prognosis (1,2). Although the incidence of IPF varies from region to region, it is incidence is 0.09-0.93 in 10000 (in ten thousand) and its prevalence varies between 0.33-4.51 in 10000 (in ten thousand) (3). The 5-year survival of IPF is 40% (4). The diagnosis of IPF is a result of the algorithm in which the HRCT and Histopathology patterns are evaluated together (5) and therefore HRCT findings are very important in the diagnosis and differential diagnosis of IPF (5,6). Chronic hypersensitivity pneumonia is an inflammatory and/or fibrotic disease that involves the lung parenchyma and small airways and frequently interferes with IPF (7). Environmental and occupational exposures may be associated with IPF as well as with CHP (8).

The mediastinum is the anatomical space located in the thoracic cavity, which is limited by the sternum anteriorly, the pleura laterally, the vertebrae posteriorly, and the thoracic inlet superiorly. The mediastinum is parted into 4 anatomical compartments; anterior, middle, posterior,

Corresponding Author: Sertan Bulut, drsertanbulut@hotmail.com
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and upper mediastinum (9). The anterior mediastinum has a structure that can be affected by various pathological conditions and easily adapt to these changes (10). The shape and physical properties of the anterior mediastinum can be easily affected by inflammatory lung diseases, tuberculosis, empyema, radiotherapy, chronic fibrotic lung diseases, previous surgery, and after steroid therapy (11-13). There are studies in which the fat ratio in the body is evaluated (the skeletal muscle index) in diagnostic processes (14).

In 2014, Hassan and Abo-Elhamd (15) investigated the properties of anterior mediastinal fat (AMF) in patients with idiopathic pulmonary fibrosis (IPF), and in 2006, Lee et al. (11) investigated the properties of AMF in patients with IPF and nonspecific interstitial pneumonia (NSIP). In 2020, González et al. (16) examined the effect of AMF on prognosis in pulmonary fibrosis patients who underwent lung transplantation. In this study, we planned to compare the properties of AMF in the patient 3 groups: patients with IPF, patients with chronic hypersensitivity pneumonia (cHP), and in the healthy control group for the first time.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences Atatürk Education and Training Hospital Clinical Researchs Ethics Committee (Date: 12/10/2021, Decision No: 2012-KAEK-15/2390). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

Patients

Patients who were evaluated and diagnosed in the 'diffuse parenchymal lung diseases multidisciplinary council' of our institution enrolled in this study. Our institution is a tertiary education and research hospital and specializes in pulmonary diseases and chest surgery. The study comprises 3 patient groups. The first group comprises 26 cases that were evaluated according to ATS/ERS criteria (5). and subsequently diagnosed as IPF. The second group comprises 19 cases who were evaluated and finally diagnosed as chronic hypersensitivity pneumonia (cHP) in the light of current guidelines (17). The third group comprises 35 control patients without any disease.

The cases included in our study are those diagnosed with IPF and cHP among all patients in the last 8 years. A total of 80 cases in the three groups were evaluated. There was no known past and/or active inflammatory or infectious disease with patients and control groups. None of the patients in the IPF and cHP groups received corticosteroids before high-resolution chest tomography (HRCT) evaluation. None of the cases had diabetes, atherosclerotic cardiovascular disease, and had no history of thoracic surgery and radiotherapy. The demographic data, BMI, smoking status, hemogram, and biochemistry analysis results of these cases were recorded retrospectively. Shape features, anteroposterior and transverse lengths, and AMF area were calculated of all cases. Pulmonary function tests (PFTs) and diffusing capacity for carbon monoxide (DLCO) results were recorded in IPF and cHP groups.

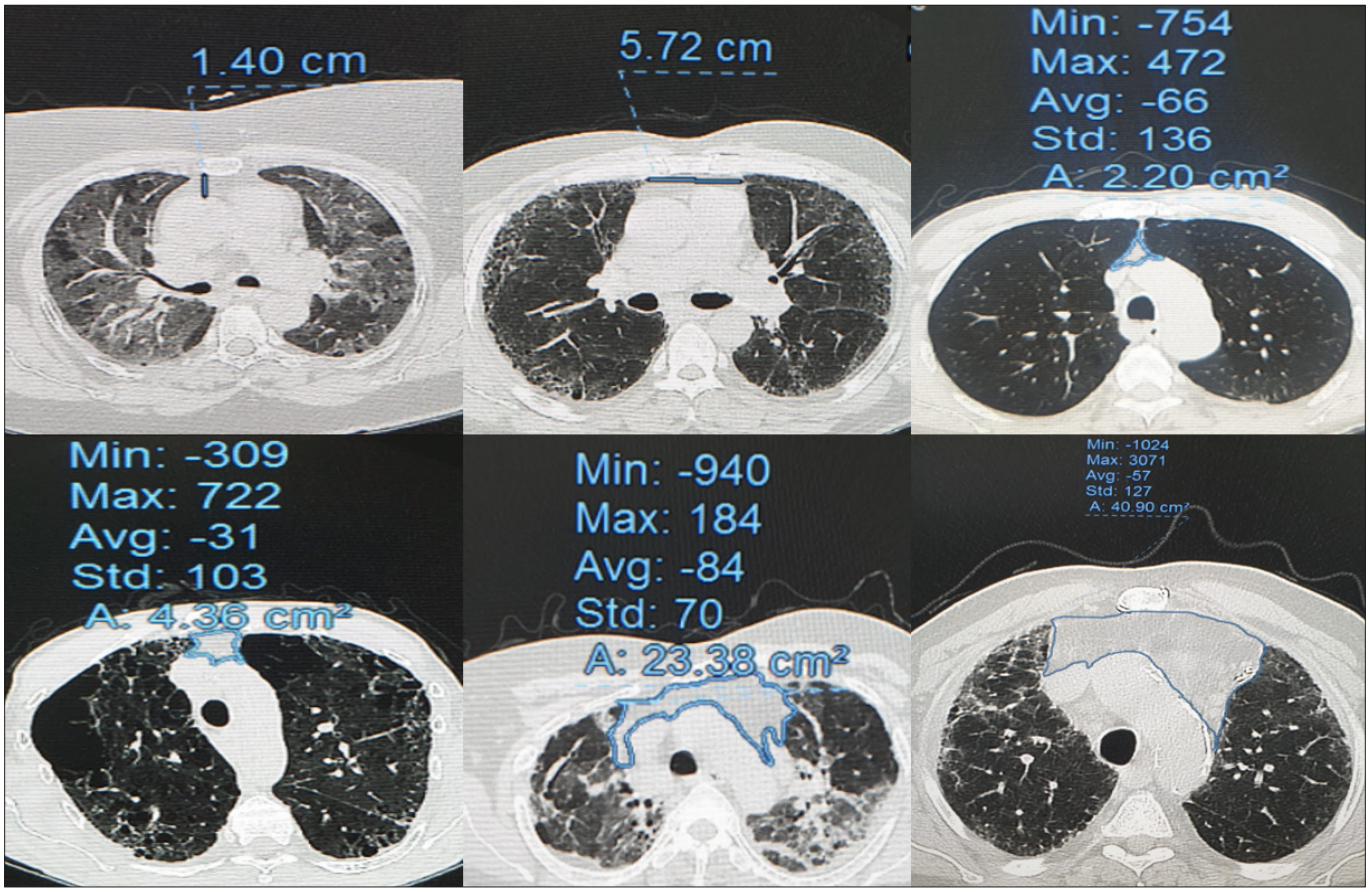
High-resolution Chest Tomography (HRCT)

All cases HRCT results analyzed. Cases were in supine position and analysis was performed without iv. contrast agents. 1.5 mm thick sections were taken in the axial plane with 128 multidetector CT device (Ingenuity CT, Philips Healthcare, Andover, MA, USA). Display parameters were Kv:120; mA:160, rotation time:0,5 s; collimation:64x0,625; FOV: 220mm. The window settings were determined as W:350, C:60 for mediastinum and W:-1600, C:-600 for parenchyma.

The shape of the anterior mediastinal fat was categorized as concave, flat, or convex at the level of the main pulmonary trunk. The anteroposterior (AP) (from the posterior wall of the sternum to the anterior wall of the ascending aorta) and transverse dimensions (the width of the posterior wall of the sternum in contact with the anterior mediastinal fat) at the level of the main pulmonary trunk was also measured (15) and the AMF area was determined manually and calculated with the CT device in cm^2.

Statistical Analysis

All the analysis was performed with SPSS System software (version 22.0). The shapes of the anterior mediastinal fat in the IPF and cHP and control groups were compared using the Chi-square test. Amounts of anterior mediastinal fat, the retrosternal AP, transverse dimensions of the anterior mediastinum, the weights, and body mass indexes (BMIs) were compared using one-way analysis of variance (ANOVA). Correlations between forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and DLCO with AP and transverse diameters and areas of anterior mediastinal fat were performed using Pearson's correlation coefficient. AUC was calculated by performing ROC analysis of AMF area, AP length, and transverse dimension values, which are our qualitative measurements for the diagnosis of IPF. Sensitivity and specificity values were determined for the statistically significant transverse dimension and AMF area values, and cut-off values were determined. Multivariate regression analyzes were performed by age, gender, smoking status, and BMIs separately, which are likely to be confounding factors for AMF shape features, length, and AMF area measurements. The fit of the models created in this regression analysis was evaluated with the Hosmer and Lemeshow test, and a p-value above 0.05 was considered a good fit. Hemogram, NLR, CRP, and albumin values were analyzed to evaluate whether



Picture 1. A. The anteroposterior (AP) (from the posterior wall of the sternum to the anterior wall of the ascending aorta), **B.** Transverse dimensions (the width of the posterior wall of the sternum in contact with the anterior mediastinal fat) at the level of the main pulmonary trunk, **C.** Concave shape, **D.** Flat shape, **E** and **F**: convex shape, *All AMF areas were determined manually and calculated with the CT device in cm^2.

there was a relationship between AMF and systemic inflammation. In addition, IPF and cHP patient groups were compared in terms of PFTs and DLCO values. The p-value less than 0.05 was considered to indicate statistically significant differences.

RESULTS

Demographic data of three groups were compared. Gender distribution was 24 males 2 females in the IPF group, 5 males 14 females in the cHP group, and 30 males and 5 females in the control group. Gender distribution was found statistically significant between the 3 groups (p=0.001). There was no statistical difference between the mean ages of cases in IPF, cHP, and control groups (67.50±12, 67.50±12, and 67.68±8.30, respectively) (p=0.67) (**Table 1**).

BMI mean value was 28.22 kg/m2 (3.56%) in the IPF group, 29.97 kg/m2 (5.99%) in the cHP group and 28.92 kg/m2 (3.29%) in the control group. There was no statistical difference between the three groups by the means of BMIs (p=0.380). There was no correlation between the smoking status of the three groups (p=0.054).

The AP dimension of AMF analyses revealed that only the cHP group's dimensions were significantly smaller than the control group's (p=0.037). In the analysis of the transverse dimension of AMF, the IPF group's dimensions were significantly greater than the control group's (p<0.0001) and greater than the cHP group's (p=0.007) and also the cHP group's dimensions were significantly greater than the control group's (p<0.0001).

Table 1. Demographic and clinical characteristics

Characteristic	IPF group (n=26)	cHP group (n=19)	Control group (n=35)	p value
Age (years) (mean±SD)	67.50±12	61.52±12.75	67.68±8.30	0.067
Male gender (n) (%)	24 (92.3%)	5 (26.31%)	30 (85.71%)	0.001*
BMI mean±sd (kg/m2)	28.22 (3.56%)	29.97 (5.99%)	28.92 (3.29%)	0.380
Smoking status (n) (%)				0.054
Current	1 (3.84%)	1 (5.26%)	5 (14.28%)	
Former	25 (96.15%)	16 (84.21%)	23 (65.71%)	
Never	0 (0%)	2 (10.52%)	7 (20.00%)	

Note. *p<0.05 BMI: Body mass index

The AMF area analyses revealed that the IPF group's areas were significantly greater than the control group's areas (p<0.0001) and greater than the cHP group's areas (p=0.0037) and also the cHP group's areas were significantly greater than the control group's (p=0.008) (**Figure 1, 2** and **Table 2**).

The AMF shape features evaluation showed a concave figure in 4 cases with cHP and 17 cases of the control group (p<0.0001), a flat figure in 3 cases IPF, 1 case with cHP, and 15 cases of the control group (p=0.002), convex figure in 23 cases with IPF, 14 cases with cHP and 3 cases of the control group (p <0.0001) (**Table 3**). In the evaluation of AMF shape properties between two groups (cHP and IPF), the concave figure was significantly more frequent in cHP group (p=0.014) (**Table 4**).

Regression analyzes of AMF shape features, lengths, and area measurements were performed in a model in which confounding risk factors such as age, BMI, smoking, and gender were included. The fit of all models created in this regression analysis was evaluated with the Hosmer and Lemeshow test. It was seen that all of them had a good model fit (p>0.05). In these regression models, none of the possible confounding factors were at the level of statistical significance (p>0.05). For example, in the evaluation of the convex shape in terms of confounding factors in **Table 5**, the Hosmer and Lemeshow test result indicated a good model fit with p=0.912, while there was no statistical significance in the risk factors examined (p>0.05).

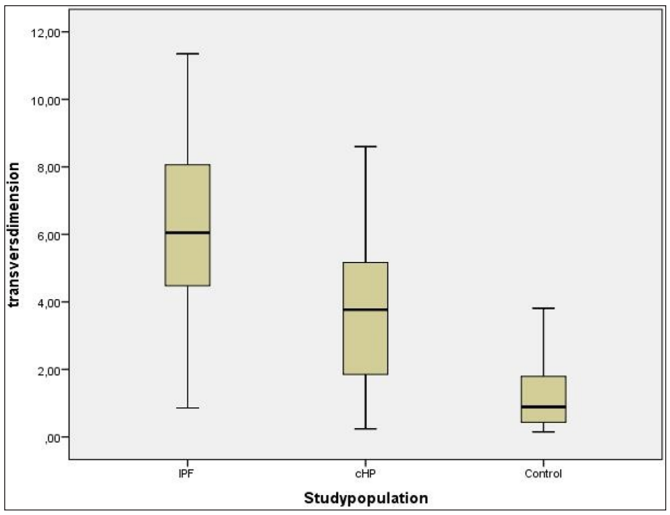


Figure 1. The IPF group's transverse dimensions were significantly greater than the control group's (p<0.0001) and greater than the cHP group's (p=0.007) and also the cHP group's transverse dimensions were significantly greater than the control group's (p<0.0001).

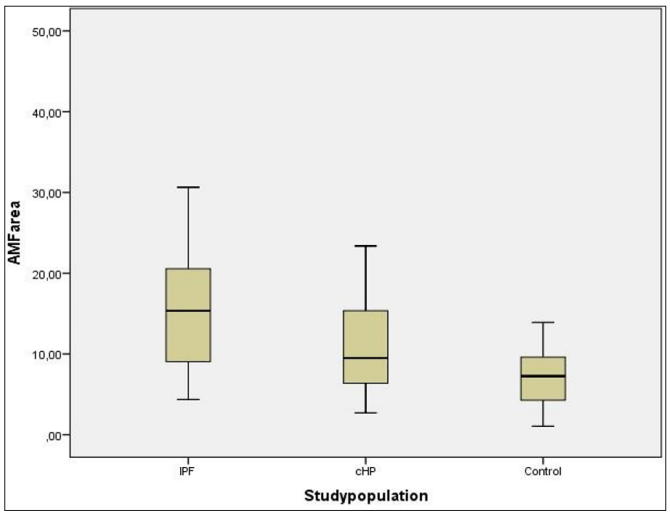


Figure 2. The IPF group's AMF areas were significantly greater than the control group's AMF areas (p<0.0001) and greater than the cHP group's AMF areas (p=0.0037) and also the cHP group's AMF areas were significantly greater than the control group's (p=0.0008).

Table 3. Different shapes of anterior mediastinum in the three groups

AMP shape	Normal n (%)	cHP n (%)	IPF n (%)	p-value
Concave	17 (48.6%)	4 (21%)	0 (0%)	0.000*
Flat	15 (42.9%)	1 (5.3%)	3 (11.2%)	0.002*
Convex	3 (8.6%)	14 (73.7%)	23 (88.4%)	0.000*

Note. *p-value < 0.05; the statistical result was obtained by the Chi-square test.

Table 4. Different shapes of anterior mediastinum in the two groups

AMP Shape	cHP n (%)	IPF n (%)	p-value n (%)
Concave	4 (21 %)	0 (0.0 %)	0.014*
Flat	1 (5.3 %)	3 (11.2 %)	0.465
Convex	14 (73.7 %)	23 (88.4 %)	0.2

Note. * p-value < 0.05; Statistical result was obtained by the Chi-square test

Table 5. The evaluation of the convex shape in terms of confounding factors with multivariate logistic regression analyze

Risk factors	OR (%95 CI)	p-value
Age	0.978 (0.932-1.027)	0.369
Gender	1.882 (0.594-5.959)	0.282
Smoking status	2.203 (0.230-21.088)	0.493
BMI	0.951 (0.839-1.077)	0.425

The Hosmer and Lemeshow test result indicated a good model fit with p=0.912 and Chi square=3.333. There was no statistical significance in the risk factors examined (p>0.05).

Table 2. Comparisons of the variables in the three groups

Variables	IPF (mean±SD)	cHP (mean±SD)	Control (mean±SD)	Normal vs cHP	Normal vs IPF	cHP vs IPF	Normal vs cHP vs IPF
Body mass index (kg/m2)	28.22±3.56	29.97±5.99	28.92±3.29	0.406	0.431	0.226	0.380
AP dimension (cm)	2.27±0.93	1.81±0.82	2.33±0.85	0.037*	0.797	0.096	0.809
Transverse dimension (cm)	6.10±2.67	3.84±2.60	1.28±1.15	0.000*	0.000*	0.007*	0.001*
Area of AMF (cm2)	15.94±8.44	11.01±6.16	7.34±3.66	0.008*	0.000*	0.037*	0.001*

Note. *p value<0.05; Data are presented as means SDs.

Correlation between the changes in the diameters of AMF with PFTs (FEV1, FVC, and DLCO) in IPF and cHP groups revealed a significant correlation between AP dimension and FEV1 and FVC (r=502, p<0.0001 and r=481, p=0.001, respectively).

As seen in **Figure 3**, ROC curves and AUC were compared between AMF area, AP length, and transverse dimension values to predict IPF diagnosis. Transverse dimension showed the best AUC=0.86, (CI 95% 0.783-0.951, p<0.0001), followed by the AMF area with an AUC=0.77 (CI95%, 0.661-0.886, p<0.0001), while AP length were not significant (p=0.551). The Transverse dimension sensitivity was 80%, specificity was 77% cutoff=3.79 cm in the diagnosis of IPF. The AMF area sensitivity was 73%, specificity was 72% cut off=9.82 cm² in the diagnosis of IPF.

Systemic inflammatory biomarkers were evaluated to determine the relationship between AMF and systemic inflammation. No relationship was found between AMF and inflammatory biomarkers, such as neutrophil, lymphocyte, neutrophil/lymphocyte ratio (NLR), CRP, and albumin levels. When the 3 groups were compared, there was a significant difference in white blood cell (WBC) levels (p=0.028), while no significant difference was observed between IPF and control groups in the subgroup analysis (9.68±2.99, 9.11±2.90, respectively; p=0.455). Also, there was no significant difference between cHP and the control group (7.84±2.46, 9.11±2.90, respectively; p=0.055).

PFTs could only be evaluated in the IPF and cHP groups, but not in the control group. A statistically significant difference was observed between the IPF and cHP groups in terms of FVC levels (2.67±0.59, 2.14±0.80, respectively; p=0.016) and FEV1 levels (2.22±0.44, 1.75±0.65, respectively; p=0.006). Also, a statistically significant difference was observed between the IPF and cHP groups in terms of DLCO levels (57.42±17.21; 77.31±35.21; respectively; p=0.016) (**Table 6**).

DISCUSSION

This is the first study in which the properties of AMF were evaluated in cHP patients and also investigated together in cHP-IPF patients. This article aimed to determine the relationship between AMF features in patients with IPF and cHP and to evaluate these features as a marker.

In this study, we defined the anatomical features of AMF in IPF, cHP, and control patients with HRCT. We showed that transverse dimension and convex shape in IPF and cHP patients were statistically significantly larger and different when compared to control patients. In this context, we have shown that transverse length and convex shape can be markers.

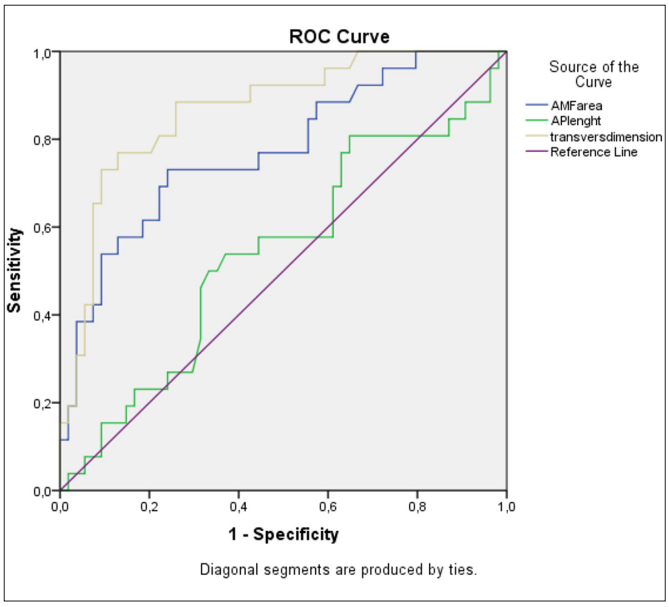


Figure 3. The ROC curves and AUC were compared between AMF area, AP length, and transverse dimension values to predict IPF diagnosis. Transverse dimension showed the best AUC=0.86, (CI 95% 0.783-0.951, p<0.0001), followed by the AMF area with an AUC=0.77 (CI95%, 0.661-0.886, p<0.0001), while AP length were not significant (p=0.551). The transverse dimension sensitivity was 80%, specificity was 77% cutoff=3.79 cm in the diagnosis of IPF. The AMF area sensitivity was 73%, specificity was 72% cut off=9.82 cm2 in the diagnosis of IPF.

Table 6. Systemic inflammation markers between three groups

Characteristic	n=80	p value
WBC unit† (mean±SD)	9.00±2.88	0.028
WBC§		
IPF vs control group		0.455
cHP vs control group		0.055
Neutrophil† (mean±SD)	6.34±2.58	0.123
Neutrophil (%)* (mean±SD)	69.71±11.10	0.736
Lymphocyte * (mean±SD)	1.83±0.78	0.113
Lymphocyte (%)* (mean±SD)	21.21±8.80	0.265
NLR† (mean±SD)	4.57±3.89	0.449
Hemoglobin* (mean±SD)	13.94±2.07	0.590
Hematocrit * (mean±SD)	43.26±5.88	0.989
Platelet* (mean±SD)	25605±90510.63	0.156
CRP† (mean±SD)	21.81±42.01	0.205
Albumin† (mean±SD)	37.11±5.66	0.965
FVC‡ (mean±SD)		0.024
IPF	2.67±0.59	
cHP	2.14±0.80	
FEV1‡ (mean±SD)		0.006
IPF	2.22±0.44	
cHP	1.75±0.65	
DLCO ‡ % (mean±SD)		0.016
IPF	57.42±17.21	
cHP	77.31±35.21	

WBC: White blood cell, NLR: Neutrophil lymphocyte ratio, CRP: C-reactive protein, FVC: Force vital capacity, DLCO: Diffusing capacity for carbon monoxide, *ANOVA, †Kruskal-Wallis test, ‡Indipendent t-test, §Mann-Whithney U Test, ||FVC and DLCO analyzed for these two groups: IPF and cHP

In addition, when we compared the AMF area, we observed that the measurements of IPF patients had the highest value. For the diagnosis of IPF, we found that the values of transverse dimension and area values were statistically significant by calculating AUC by ROC analysis of AMF qualitative measurements. We determined the cut-off values of these two data as 3.79 cm and 9.82 cm², respectively.

In previous studies examining the properties of AMF, the relationship between AMF and systemic inflammation was never examined (11,15,16). This is the first study evaluating the properties of AMF with systemic inflammation in both IPF and cHP patients, and it has been shown that there is no relationship between AMF and systemic inflammation.

AMF characteristics can be affected by infectious and inflammatory lung diseases, thoracic surgery and thoracic radiotherapy, and steroid therapy given for any reason (10-12). Likewise, intrathoracic fat can be affected by obesity as well as diabetes and is associated with ASHH (18). We did not include the cases with the above-mentioned conditions.

In previous studies, the IPF group's AMP transverse length tended to be taller, and AP length was shorter compared to the control group (11,15). In our study; Transverse length and AMF area were found to be consistent with previous studies in both IPF and cHP groups, which were statistically significantly different from the control group.

We also determined a cut-off value using qualitative measures of AMF that had not been evaluated in previous studies. In the diagnosis of IPF for the transverse dimension our calculated cut-off value=3.79 cm, sensitivity 80%, specificity 77% (p<0.0001), and for the AMF area cut-off value=9.82 cm², sensitivity 73%, specificity 72% (p<0.0001).

Lee et al. (11) found that in IPF patients, AMF tended to be transversely taller and shorter at the AP plane compared with the control group. They explained this result with the following mechanism: "The widening of the transverse dimension and the shortening of the anteroposterior dimension of the anterior mediastinal fat seem to be bilateral tensile forces induced by subpleural fibrosis of the lung tissue that was adjacent to the mediastinum.". In our study, transverse length and AMF area feature support this mechanism. In our study, the fact that AP length is statistically less than normal controls in cHP, which can also be a fibrotic disease, also supports this mechanism.

We showed that systemic inflammatory markers were similar in all 3 groups. For all these reasons, we also support this possible mechanism. However, interestingly, we cannot explain the similarity of the AP length in the IPF and the control group, which is revealed in our study, by any mechanism.

In previous studies, the relationship between AMF and systemic inflammation was not discussed. In our study, systemic inflammatory markers were evaluated to determine the relationship between AMF and systemic inflammation. No relationship was found between AMF and inflammatory biomarkers, such as neutrophil, lymphocyte, neutrophil/lymphocyte ratio (NLR), CRP, and albumin levels.

In previous studies, AMF shape features tended to be convex in the IPF group and concave in normal healthy subjects (11,15,16). In our study, it was found as concave (p<0.0001), flat (p=0.002), convex (p<0.0001) for 3 groups. In the subgroup analysis, the cHP group tended to be concave in terms of AMF shape properties compared to the IPF group (p=0.014).

As a conclusion, we think that the transverse length, AMF area, and shape characteristics of AMF can be evaluated as a radiological marker for differential diagnosis of IPF and cHP, whose differential diagnosis may be difficult. It has been observed that both the transverse length and AMF area can take greater values in IPF patient groups than in the cHP group.

In the analysis of PFTs between the IPF and cHP groups, we found a significant difference (2,67±0,59; 2,14±0,80; respectively, p=0,024). The cHP patients were symptomatic and we used their PFTs before steroid therapy. Because of this, compared to the IPF group, PFTs were significantly low and recovery was expected after steroid therapy (19). Also, a significant difference was observed between the IPF and cHP groups in terms of DLCO levels (57,42±17,21; 77,31±35,21; respectively; p=0,016). This is consistent with previous literature data (20).

Hassan et al. (15) reported that AMF transverse length was negatively correlated with pulmonary functions and AP length was positively correlated in patients with IPF. In our study, we found a relationship between AP length and FVC and FEV1 (r=502, p<0.0001 and r=481, p=0.001; respectively). Interestingly, there was no relationship with PFTs in terms of transverse length and AMF area in both case groups.

This study's limitations were being a retrospective single-center study and a relatively limited number of patients.

CONCLUSION

Qualitative and quantitative characteristics of AMF can be an additional help in distinguishing from normal healthy adults during radiological evaluation while making cHP and IPF diagnoses. In addition, quantitative

measurements of AMF can help us to distinguish between two clinical entities such as IPF and cHP, which can sometimes be difficult to distinguish from each other. We recommend that these results could be supported by prospective studies with a higher number of cases.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Atatürk Education and Training Hospital Clinical Research Ethics Committee (Date: 12/10/2021, Decision No: 2012-KAEK-15/2390).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Short-and long-term results of ultrasound-guided fine-needle aspiration and steroid injection in the treatment of ganglion cysts

Taha Yusuf Kuzan[1], Osman Yüksel Yavuz[2]

[1]Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Department of Radiology, İstanbul, Turkey
[2]Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Department of Orthopedics and Traumatology, İstanbul, Turkey

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ABSTRACT

Objective: To determine the efficacy and safety of percutaneous aspiration and steroid injection treatment for ganglion cysts and retrospectively evaluate the size change in ganglion cysts during follow-up.

Material and Method: All patients who underwent percutaneous aspiration and steroid injection treatment for ganglion cysts between January 2019 and February 2020 were included in the study. Demographic characteristics and clinical signs and findings of the patients were obtained from electronic patient records. Treatment response was classified as "excellent," "good," and "poor" at one month and one year according to ultrasound measurement.

Results: Ganglion cyst aspiration and steroid injection were successfully performed in 37 (86.0%) of 43 cases. A total of 28 cases with short- and long-term follow-ups were included in the final analysis. All the cases had cosmetic complaints before the treatment, and seven had pain and four had limited range of motion. Early treatment response was excellent in 7 (25.0%) patients, good in 14 (50.0%), and poor in 7 (50.0%). Late treatment response was excellent in 18 (64.3%) patients, good in 3 (10.7%), and poor in 7 (25.0%). After the procedure, mild pain lasting less than two days developed in the cyst area in half of the patients. Skin color change was observed in two cases in the first-month follow-up.

Conclusion: Ultrasound-guided fine-needle aspiration and steroid injection with the right technique is an alternative cost-effective method to surgery that can be successfully applied in the treatment of ganglion cysts with low side effects and relatively good results.

Keywords: Ganglion, cyst, aspiration, steroid, injection

INTRODUCTION

Ganglion cysts are benign "tumor-like" fluid lesions that develop because of mucinous involution of collagen structures; they may originate from different parts of the body in relation to the musculoskeletal system, such as joint capsules, muscles, tendons, and tendon sheaths (1,2). They are most often seen on the dorsal side of the wrist (70%), followed by the volar side of the wrist (20%), and in the tendon sheath of the fingers, while ganglion cysts originating from other joints are relatively rare (3,4). Most ganglion cysts are asymptomatic except for swelling. When symptomatic they result in pain, effusion, joint tenderness, and limited range of motion (2). Although ganglion cysts are non-malignant cystic masses, most patients seek treatment because of their cosmetic appearance or because of concerns about their ganglion enlargement.

Treatment options include non-invasive follow-up, conservative treatment, and surgical excision (5). Although there are publications on conservative care of ganglion cysts, there is scarce information in the literature on the results of treatment with ultrasound-guided percutaneous aspiration and steroid injection (6).

Our aim in this study is to determine the efficacy and safety of treatment in patients who underwent percutaneous aspiration and steroid injection due to ganglion cysts in our center, and to evaluate retrospectively the size change in ganglion cysts during the follow-up period.

Corresponding Author: Taha Yusuf Kuzan, tykuzan@gmail.com
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MATERIAL AND METHOD

The study was carried out with the permission Sancaktepe Sehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 2021, Decision No: 2021/89). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection and Study Design

All patients who underwent percutaneous treatment for ganglion cysts in the interventional radiology department of our center between January 2019 and February 2020 were included in this retrospective study. Demographic, clinical, and radiological characteristics and treatment and outcomes data were obtained from electronic medical records. The dominant hand of the patients was also noted. All patients included in the study underwent ultrasonography (USG) by a general radiologist for ganglion cysts. The ganglion cyst diagnosis on ultrasound was made by showing the connection of the anechoic-hypoechoic cyst with a typical localization, well-defined margins, and acoustic enhancement with the adjacent joint. In doubtful cases on USG, the diagnosis was confirmed by magnetic resonance imaging (MRI). The definitive diagnosis was confirmed by thick and clear or translucent gelatinous fluid aspirated from the cysts. Before the procedure, the volume of the cysts was calculated and recorded on USG (with the formula: volume = width×depth×length×0.52). The study did not include cysts with a long axis shorter than 1 cm and patients who could not be aspirated or did not receive a steroid injection after aspiration.

The patients were called for follow-up one month and one year after the procedure to evaluate their response to early and long-term treatments, respectively. USG was conducted again to allow for the measurement of volume and comparison with the previous USG. Treatment response was defined by USG volume measurement: 1: Excellent - complete regression without induration, 2: Good - >50% volume regression, 3: Poor - <50% volume regression or size increase. The interventional radiologist made baseline and follow-up USG measurements.

Cases with short-term and long-term follow-ups were included in the final analysis. The flow chart of the study is shown in **Figure 1**.

Ultrasound-guided Fine-needle Aspiration and Steroid Injection Technique

Ganglion cyst aspiration and steroid injections were performed by a radiologist with seven years of experience in all cases. All procedures were performed under USG guidance using a linear 7.2–14 MHz probe. Before the procedure, the cyst was detected using the ultrasound probe, and a local anesthetic was applied to the skin. Having allowed the appropriate time for the topical anesthesia to be effective, the skin was then cleaned with iodine solution. Before the cyst was punctured, it was softened by applying light external pressure. Then, under USG guidance, the center of the cyst was entered using a 21G fine needle, and the cyst fluid was aspirated as much as possible with a 10 ml disposable luer-lock injector. In cases where aspiration of the entire cyst was not possible, external pressure was applied and the entire contents of the cyst were cleaned out. After aspiration, an intralesional 1 ml steroid (Diprospan, Betamethasone dipropionate: 6.43 mg (5.0 mg betamethasone equivalent) + Betamethasone sodium phosphate: 2.63 mg (5.0 mg betamethasone)) was injected into the cyst through the same needle. After the procedure, a pressure bandage was applied to the cyst area. If pain then occurred, oral paracetamol was recommended. An example of a percutaneous treatment procedure and images of a ganglion cyst are shown in **Figures 2** and **3**.

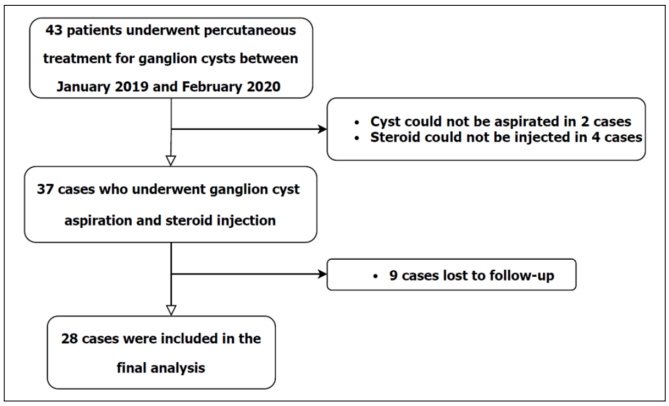

Figure 1. Flow chart of the study

Statistical Analysis

Descriptive analyzes were performed for patient characteristics. Normality control of continuous variables was done with Shapiro Wilk test. Normally distributed continuous variables were expressed as ± standard deviation (SD), non-normally distributed continuous variables were expressed as median and range. Categorical variables were shown as percentages. Wilcoxon Signed-Rank test was used for cyst volume comparisons. P value < 0.05 was considered statistically significant and analyzes were performed using SPSS statistics 23.0 software (IBM Corp., Armonk, NY, USA).

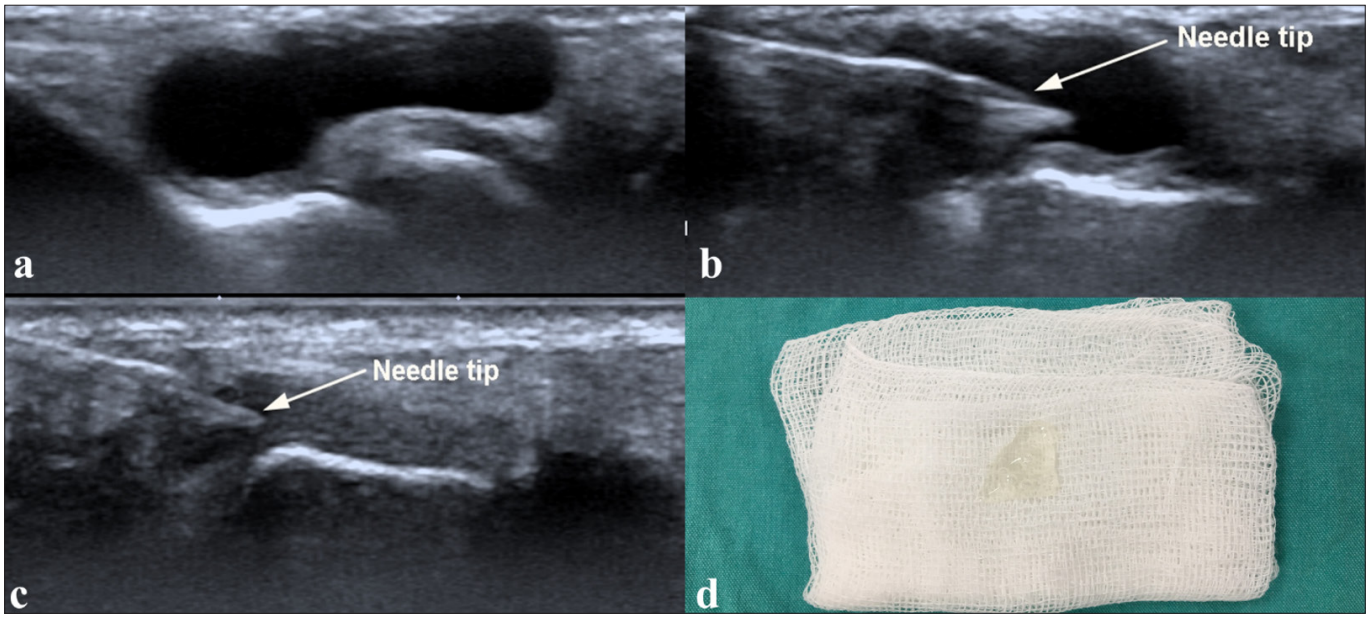

Figure 2. Ultrasonography image of the wrist ganglion cyst before the procedure (a). Under the guidance of ultrasonography, a 21 gauge needle is inserted into the central part of the ganglion cyst (b), the entire cyst content is aspirated (c), and then steroid injection is performed through the same needle tract. Clear and viscous translucent gelatinous fluid content of the ganglion cyst is seen (d).

RESULTS

A total of 28 cases with short- and long-term follow-ups were included in the final analysis. The age of the cases ranged from 16 to 60, with a median of 29.9 years. Ten cases (35.7%) were male and the remaining (64.3%) were female. The cysts were located in the dorsal of the right hand in 17 (60.7%) cases, the left hand dorsal in 8 (28.6%) cases, the left foot dorsal in 2 (7.1%) cases, and the right foot dorsal in 1 (3.6%) case. 7 of the cases had pain and 4 had limited range of motion while all of the cases had cosmetic complaints before the treatment. Of the cases with wrist ganglion, 20 were right hand dominant and 5 left hand dominant.

In 2 of the cases that were not included in the final analysis, the cyst content could not be aspirated completely as it was too viscous, apart from this, cyst aspiration was technically successful in 41 (95.3%) of 43 patients. Steroid injection could not be performed after aspiration in one case because the needle tract was lost after aspiration and in 3 cases because the aspiration volume was too small. As a result, aspiration and steroid injection of ganglion cysts were technically successful in 37 (86.0%) of 43 cases. Nine out of 37 patients were not included in the final analysis because they did not participate in the follow-ups.

Early and late treatment responses are summarized in **Table 1**. The difference between the early (383.3±631.1 mm³) and late (282.9±618.1 mm³) volumes compared to the baseline (was 995.5±736.8 mm³) volume was quite significant ($p<0.001$ and $p<0.001$, respectively). However, the difference in volume between the early and late periods was not significant ($p=0.530$).

Table 1. First month and first-year treatment response status

	1st year follow-up			
	Excellent	Good	Poor	Total
1st month follow-up				
Excellent	5	1	1	7
Good	9	1	4	14
Poor	4	1	2	7
Total	18	3	7	28

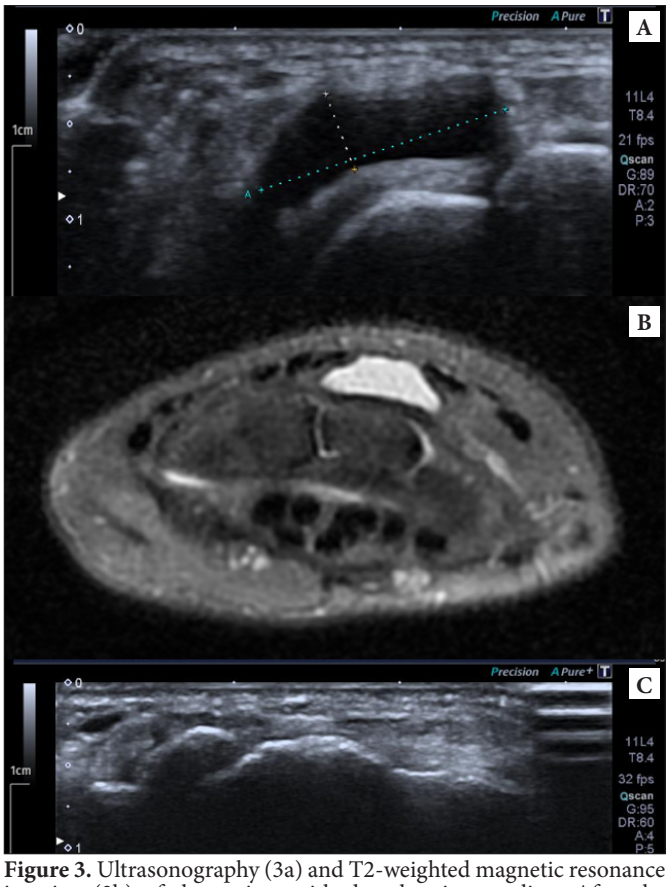

Figure 3. Ultrasonography (3a) and T2-weighted magnetic resonance imaging (3b) of the patient with dorsal wrist ganglion. After the percutaneous treatment, the first-month follow-up ultrasonography (3c) showed that the cyst had completely disappeared.

Mild pain lasting less than 2 days developed in the cyst area in half of the cases after the procedure. In 2 cases, skin color change was observed in the 1st-month follow-up. In the 1st year follow-up, the color change improved in one of the cases.

DISCUSSION

In this study, the outcomes of percutaneous aspiration and steroid injection in the treatment of ganglion cysts were analyzed. Both the early and late responses of aspiration and steroid injection were found to be acceptable in three out of four cases.

The reason for the formation of ganglion cysts is not known precisely; one of the theories is that ganglion cysts are caused by chronic inflammation. Based on this assumption, steroid injection is preferred for the treatment of ganglion cysts (7). However, conflicting results have been reported on the effectiveness of this treatment method. In addition, there is no standard for the type, amount and method of administration of the steroid. The aim of this study was planned to clarify these points.

Similar to the literature, the patients included in the study were mostly women, and their lesions were located mostly in the dorsal wrist. What is remarkable in our study was that the patients' ganglion cysts were twice as likely to be located in the right hand as in the left hand. Turgut et al. similarly reported more ganglion cysts in the right hand and associated this with the dominant hand (8). In our study, most of the patients were right-hand dominant; thus, their ganglion cysts may be related to repetitive injury, which is one of the formation theories of ganglion cysts (9).

Some researchers have suggested that 40-58% of ganglion cysts can regress spontaneously, and therefore, patients who do not request intervention can be followed (10). However, as in our study, patients often want to be treated primarily for cosmetic reasons and less often because the ganglia are symptomatic. Although different surgical and non-surgical methods are used to treat ganglion cysts, there is no standard for the management of ganglion cysts. Treatment options include open or arthroscopic surgical excision, observation and percutaneous methods such as aspiration with or without steroid or hyaluronidase injections and sclerotherapy (4), but the treatment option that is best for ganglion cyst management remains uncertain.

The literature reports different results in the treatment of ganglion cysts with both different and similar methods. In a review evaluating the efficacy of percutaneous methods, it was shown that more than half of ganglion cysts recur after aspiration alone (4). Although Mackie et al. (11) showed that sclerosis of ganglion cysts with sodium tetradecyl disulphate resulted in recurrence in up to 94% of cases, other studies have found that sclerosis with newer methods has very low failure rates (12). While Becker et al. (13) claim that aspiration and steroid injection provide resolution as high as 87%, Varley et al. (6) claim that steroid injection does not make any additional contribution to aspiration. In our study, we attributed the fact that the majority of patients who reported good results in the early period, showed excellent results in the late period to the long-term effect of steroid injection. In studies evaluating the results of percutaneous aspiration and steroid injection of ganglion cysts, the recurrence rate was found to be between 35% and 83% (14). In our study, an acceptable ganglion cyst resolution of 75% was achieved in the first year, similar to the results of Becker et al. (13).

Some previous studies have found that the recurrence rate after open or arthroscopic surgery ranges from 0% to 31.2% (4,15,16). Although arthroscopic surgery is among the treatment options, in a wrist arthroscopy series that included 2,420 patients, an eight-fold increase in ganglion cyst development was reported after arthroscopy compared to the normal population (17). Recurrence of surgery was found to be lower in two randomized controlled studies that compared surgery with percutaneous treatment (18,19). Although the recurrence of surgery shows a variable range, the general opinion is that the recurrence of surgery is less than aspiration, but the complication rates are significantly higher in surgery compared to aspiration (0–56% versus 0–12%) (4,16,20).

In our study, short-term mild pain was observed in one-fourth of the patients after the procedure. In 2 cases, skin depigmentation was observed. Skin depigmentation is one of the side effects of steroids and has been observed in similar studies using steroid injection (21). In this study, the patients who developed pain and depigmentation were the patients whose aspiration volume was less than the injected steroid. Therefore, the authors agree that side effects such as post-procedure pain and depigmentation are due to the injection of the steroid coming out of the cyst cavity. To reduce the side effects that develop due to the injected steroid; multiple punctures should not be performed on the cyst to be aspirated, the same inlet tract should be used for steroid injection, and most importantly, steroid injection should not be made more than the aspirated ganglion content. Because steroids that exceed the cyst capacity or spread out of the cyst cavity can cause pain, skin atrophy and depigmentation.

Although the treatment success of surgical excision is relatively high, the complications of the procedure are serious and excessive compared to percutaneous methods.

In recurrent cysts, reoperation is not always possible. For this reason, ultrasound-guided percutaneous aspiration of ganglion cysts can be performed quickly, safely, and cheaper in outpatient settings (22). Another advantage of ultrasound-guided aspiration is that the procedure is reproducible.

However, some limitations should be noted. First, some patients avoided coming to the hospital and did not participate in the follow-up because the study time coincided with the pandemic period. This resulted in a relative decrease in the number of patients included in the final analysis. Second, MRI was not performed in all of the patients before the procedure, and the diagnosis was made only by USG in these patients. Another limitation is the relative shortness of the follow-up period.

CONCLUSION

As a result, ultrasound-guided fine-needle aspiration and steroid injection with the right technique; is an alternative cost-effective method to surgery that can be successfully applied in the treatment of ganglion cysts with low side effects and relatively good results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 2021, Decision No: 2021/89).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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The effect of COVID-19 pandemic on life quality of dental professionals

Eda Arat Maden[1], Buğra Özen[2], Ceyhan Altun[2]

[1]Sarıyer Oral and Dental Health Center, Department of Pediatric Dentistry, İstanbul, Turkey
[2]İstanbul Health and Technology University, Faculty of Dentistry, Department of Pediatric Dentistry, İstanbul, Turkey

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ABSTRACT

Introduction: The coronavirus disease of 2019 (COVID-19) pandemic has become the most challenging issue for dental professionals all over the world. The majority of epidemiological reports focus on quality of life and health of general health care workers during the COVID-19 pandemic. In this study, it was aimed to assess the effects of the pandemic on dental professionals' quality of life.

Material and Method: After the vaccination of healthcare workers in Turkey during the COVID-19 pandemic, a descriptive cross-sectional study of 487 dental professionals was carried out by the researchers. Short Form-36 (SF-36) which is based on eight dimensions of health were used to assess dental professionals' quality of life. The data was collected using an electronic questionnaire distributed online. The participants were asked to indicate their socio-demographic data, their practices regarding the COVID-19 pandemic and whether they had contracted the COVID-19 disease.

Results: The quality of life of all participants was moderately disrupted during the COVID-19 pandemic with a mental health score of 51.32 (±20.66) and a physical health score of 72.9 (±16.73). Participants who had case tracing duty during the COVID-19 pandemic scored lower with 45.83 (±20.08) in mental health and 66.94 (±18.47) in physical health. Overall, COVID-19 pandemic has a serious impact on the quality of life and and this impact is more marked in dental professionals with fewer years of experience and those who had case tracing duty during the COVID-19 pandemic.

Conclusion: The results confirm the need to pay attention to the health of dental professionals who had case tracing duty during the COVID-19 pandemic. The results also point out that dental professionals who are recent graduates and working in the public sector may be more likely to have well-being problems due to the COVID-19 pandemic.

Keywords: COVID-19, dental professionals, health concerns, life quality

INTRODUCTION

Since the first COVID-19 confirmed case was diagnosed in December 2019 in Wuhan, China, all aspects of life have been influenced worldwide (1). This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), and its transmission can occur after close contact with infected individuals via their body fluids and the respiratory droplets and aerosols (2). Dental treatment can create large amounts of aerosols and droplets mixed with the patient's saliva or blood (3). Since SARSCoV-2 is detected in the saliva of infected individuals, this poses a risk to dentists (4). The oral mucosa has been accepted as a high-risk route of transmission for COVID-19, limiting dental activities to treat urgent and emergency procedures to minimize the production of drops or sprays (5). Dental professionals are concerned about contamination, not only for themselves but also for their families and colleagues. Dentists in many countries had to stop working during the quarantine period until notice stating otherwise. However, they also have had major concerns about the financial consequences of a lockdown (6). Isolation and its financial impact led to physical and psychological pressure, and mental health (MH) problems in dental professionals (5). Besides, due to insufficient number of healthcare providers (HCPs) and the large number of patients, the leaves of many members of medical staff were canceled, and some oral health providers were given extended shifts where some of them had to work in case tracing. In the fight against the COVID-19 pandemic in Turkey, dental professionals were assigned to screen suspected cases, provide consultation, and

Corresponding Author: Eda Arat Maden, edamaden1980@gmail.com
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conduct swabs, and played a major role in controlling the epidemic. During this pandemic, a combination of the burden brought about by the pandemic and changes in the daily work routine may have caused poor quality of life to the dental professionals in Turkey.

There are studies in the literature measuring the psychological effects of the COVID-19 pandemic period on healthcare workers (7,8-11). In these studies, it has been shown that the mental health of healthcare professionals is adversely affected due to factors such as long working hours, the risk of disease transmission and transmission to the close circle of friends and family, uncertainties regarding the pandemic, and duties carried out with additional personal protective equipment (8). There are studies showing that all these events cause reluctance to go to work and even leave the profession (12). Healthcare workers have become more susceptible to contracting the disease, as they have to continue their duties while the uncertainty about the epidemic continues. This uncertainty negatively affects mental health and general health. It is therefore reasonable to assume that the health consequences of the pandemic are not limited to those directly related to havig the infection (13).

The majority of research on the effect of COVID-19 infection on dentistry has been focused on practice of dentistry and the measures for the prevention of COVID-19. Only a few studies have evaluated the effects of the COVID-19 outbreak on life quality of dental professionals. Knowledge on the psychological impact of the pandemic on dental personnel is important both to facilitate the optimal treatment of patients as well as the psychological wellbeing of professionals. However, studies investigating the COVID-19 outbreak related concerns and emotional reactions among dental staff from different countries and populations are still required (13). Therefore, the aim of the present study was to explore the factors that influence the physical and psychological impact among dental professionals in relation to background characteristics; their work situation, years of practice, extended shifts like case tracing, and whether having contracted COVID-19 before being vaccinated.

MATERIAL AND METHOD

For this study, permission was obtained from the COVID-19 Scientific Research Evaluation Commission established under the Ministry of Health, General Directorate of Health Services. Ethical permission required for the study to be carried out was obtained from Gaziosmanpaşa Training and Research Hospital, Medical Researchs Local Ethics Committee (Date: 17.03.2021, Decision No: 2021-243). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This report is based on a questionnaire conducted from March 26 to April 26, 2021, among 487 Turkish dental professionals including those doing post-graduation studies, working in government, private and other health sectors. No setting or location was determined for the study since it was carried out online. Since it is impossible to reach the whole poulation, the lowest number of dental professionals to be included in the study and the sample size were calculated as a minimum of 398 when α=0.05, effect size=0.25 and the power of the test was 0.80 by the power analysis before the study.

A questionnaire was designed with guidance from the relevant sources and based on experts' opinions (attending dental professionals). It includes 12 questions aimed at obtaining information about the socio-demographic and occupational characteristics of the participants. The questionnaire form used in the study consists of two parts. In the first part, the descriptive and occupational characteristics of the participants such as age, gender, specialty and the unit they work in, health conditions (symptoms/signs relative to the COVID-19 flu), working condition, and knowledge and self-perceived risk of infection were included. In the second part, the Short Form-36 (SF-36), a survey was used to evaluate the quality of life of dental professionals. A brief introduction was presented at the beginning of the survey to inform the respondents of the purpose and content of this study, and electronic informed consent was obtained as to whether they agreed to complete the questionnaire. The dental professionals were asked to participate in the study via the internet (e-mail or social media) and were asked to distribute the survey among other colleagues at their convenience. Altough 610 participants were invited to take part in the survey, 487 of them completed the questionnaires, which resulted in a response rate of 79.8%.

Short Form 36 (SF-36) Life Quality Scale

It is an individual assessment scale developed by Ware et al., in 1987 to examine the general population in the monitoring of health policies in clinical practices and research (14). The Turkish validity study of the scale was conducted in 2018 by Bilir and İçağasıoğlu (15). This survey had 36 items for evaluating the status of the aspects related to physical and mental health. The main aspect of physical health had 4 subgroups, i.e., physical functioning, pain, general health and limitations due to physical health. Limitations due to emotional problems, emotional well-being, social functioning, and energy/fatigue were the subgroups included in the mental health aspect of quality of life. The parts assessing physical and mental health were scored separately from 0 to 100. Lower scores indicated severe impairment and higher scores represented better functions in each item. Increasing scores indicate good quality of life (15).

Statistical Analysis

All data were transferred from Google forms into Microsoft Excel (Microsoft Corp, Redmond, WA) and analyzed with IBM SPSS Statistics 22 (SPSS IBM, Turkey). The suitability of the parameters to the normal distribution was evaluated by Kolmogorow-Smirnov and Shapiro Wilks test. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency), Kruskal Wallis test was used in the comparison of more than two groups of parameters in comparison of quantitative data and Dunn's test was used to determine the group that caused the difference. Mann Whitney U test was used for comparisons of parameters between the two groups. Person correlation analysis was used in examining the relationship between the parameters conforming to the normal distribution, and Spearman's rho correlation analysis was used in examining the relationship between the parameters not conforming to normal distribution. Significance was assessed at the $p < 0.05$ level.

Table 1. Background characteristics of respondents

	Min.-Max.	Me.±S.D.
Age	20-75	37.41±11.76
	n	%
Gender (n=486)		
Male	149	30.7
Female	337	69.3
Age (n=484)		
20-29	180	37.2
30-39	110	22.7
40 and over	194	40.1
Work sector (n=485)		
Private dental office	132	27.2
Private dental polyclinic	114	23.5
Private dental hospital	17	3.5
State university	132	27.2
Foundation university	50	10.3
Govermental oral and dental health center	30	6.2
Other official institutions	10	2
Years of experience (n=484)		
1-5	181	37.4
6-10	70	14.5
11-15	34	7
16-20	48	9.9
21-30	95	19.6
30 and over	56	11.6
Title (n=485)		
Dentists (Dt)	163	33.6
Research assistant (Phd)	138	28.5
Specialist	44	9.1
Doctor	48	9.9
Assistant professors	53	10.9
Associate professor	39	8
Speciality (n=460)		
Oral and Maxillofacial Surgery	11	2.4
Oral and Maxillofacial Radyology	4	0.9
Endodontics	14	3
Orthodontics	16	3.5
Periodontology	7	1.5
Prosthetic dentistry	8	1.7
Restorative dentistry	8	1.7
Pediatric Dentistry	261	56.7
No Specialization/PhD	128	27.8

RESULTS

Overall, 487 dental professionals filled the questionnaire. Among all the participants, 149 (%30.7) were male, and 337 (%69.3) were female. The average age was 37.41±11.76 years. Background characteristics of respondents were given in **Table 1**.

9.8% of the participants have had COVID-19. Fatigue (89.4%) and headache (53.2%) were the most common symptoms related to COVID-19 (**Table 2**). 72.6% of dental professionals cared for all patients, 24.7% only cared for emergency patients, and 2.7% did not admit any patients. While 8.2% of the participants had extra shifts like case tracing during the COVID-19 pandemic whereas 91.8% did not. While 92.4% believe that the infection caused by COVID-19 is a risk to the dentist, 0.6% do not believe this and 7% partially believe such a thing (**Table 2**).

Table 2. Distribution of work-related data

	n	%
Contracting the COVID-19 disease (n=482)		
Yes	47	9.8
No	435	90.2
Symptoms		
Yes	440	90.3
No	47	9.7
Symptoms (n=47)		
Fever	13	27.7
Cough	17	36.2
Fatigue	42	89.4
Short Breath	14	29.8
Nasal congestion	12	25.5
Headache	25	53.2
Rhinorrhea	5	10.6
Sore throat	14	29.8
Widespread pain	18	38.3
Diarrhea	12	25.5
Conjunctivitis	5	10.6
Emergency patients only (n=485)		
Yes	120	24.7
No	352	72.6
I do not accept any patients	13	2.7
Case tracing during Covid-19 pandemic (n=485)		
Yes	40	8.2
No	445	91.8
Believing that infection by COVID-19 is a risk to the dentist (n=486)		
Yes	449	92.4
No	3	0.6
Partially	34	7
Confident that being infected with COVID-19 can be avoided during the study (n=484)		
I am not confident	268	55.4
I am confident enough	92	19
I'm a little confident	98	20.2
I think I can be protected with the vaccine	26	5.4

The minimum, maximum, mean, standard deviation and median values of the sub-dimensions of the quality of life scale are as seen in **Table 3.** In the relationship between gender and quality of life; physical aspect, mental aspect and SF-36 overall scores of female dental professionals were significantly higher than those of males' (p:0.001; p<0.05). In the relationship between age and quality of life, there was a positive, 12.3%, and statistically significant relationship between age and physical aspect score values (p:0.007; p<0.05). There was a positive, 31.6%, and statistically significant relationship between age and mental aspect score values (p:0.000; p<0.05). There was a positive, 25.6%, and statistically significant relationship between age and SF-36 general score (p:0.000; p<0.05). The physical aspect scores of dental professionals aged between 20 and 29 were significantly lower than the scores of dental professionals aged betweenn 30 and 39 and those aged 40 and over (p1:0.001; p2:0.000; p<0.05). Mental aspect scores of dental professionals over 40 years of age were significantly higher than those of dental professionals aged 20-29 and 30-39 years (p1:0.000; p2:0.004; p<0.05).

Table 3. Minimum, maximum, mean, standard deviation and median values of the sub-dimension scores of the quality of life (SF-36) scale

	Min.	Max.	Me.±S.D.	Median
Physical functioning	0	100	85±17.54	90
Limitations due to physical health	0	100	65.5±38.17	75
Pain	22	90	73.56±16.15	74
General health	25	100	67.54±16.01	67
Energy/fatigue	0	95	42.36±19.87	40
Social functioning	0	100	52.26±29.57	50
Emotional well-being	0	100	49.9±40.96	33.33
Limitations due to emotional problems	12	100	60.74±17.77	64
Physical aspect	17.75	97.5	72.9±16.73	77.25
Mental aspect	8	94.75	51.32±20.66	50.08
SF-36 General	20.94	96.13	62.11±16.77	61.73

There was a statistically significant difference between the SF-36 general scores of the dental professionals according to the institution they work at (p:0.000; p<0.05). SF-36 general scores of dental professionals working in a private dental office were significantly higher than the scores of dental professionals working in foundation universities and other institutions (p1:0.048; p2:0.003; p<0.05). SF-36 general scores of dentists working in a private dental polyclinic were significantly higher than those of dental professionals working in other institutions (p:0.009; p<0.05).

There was a statistically significant difference between SF-36 general scores of the dental professionals according to years of experience (p:0.000; p<0.05). SF-36 general scores of dental professionals with an experience of 1-5 years were significantly lower than the scores of dental professionals with with an experience of 6-10 years, 16-20 years, 21-30 years and more than 30 years (p1:0.004; p2:0.000; p3:0.000; p4:0.000; p<0.05).

There was no statistically significant difference between the fields of specialization in terms of SF-36 general scores (p>0.05). In the COVID-19 pandemic, the physical aspect scores and SF-36 general scores of the dental professionals who were on case tracing duty were statistically significantly lower than those of the dental professionals who were not (p:0.025; p<0.05).

In the study, it was found that the SF-36 overall scores of those who think that they can be protected from COVID-19 with vaccination were statistically significantly higher than those who were not confident that they can avoid COVID-19 and those who were a little confident in doing so (p1:0.000; p2:0.002; p<0.05). Moreover, it could be concluded from the study that the SF-36 overall scores of those who were not confident in avoiding COVID-19 were statistically significantly lower than those who were sufficiently confident and a little confident (p1:0.000; p2:0.021; p<0.05).

DISCUSSION

To the best of our knowledge, this study is the first of its kind to focus on the quality of life in dental health professionals during the recent COVID-19 outbreak. We present this data on general quality of life disruptions to provide evidence on the health of dental professionals during this COVID-19 crisis. However, most studies on quality of life during the COVID-19 pandemic have been conducted among frontline health care workers, and more studies among dental professionals are required.

Although the well-being and emotional resilience of healthcare workers are essential components of maintaining health services during the COVID-19 pandemic, it has been observed that healthcare workers experience serious psychological problems and are at risk for mental health during this period (16). A recent survey reported an increased risk of depression, anxiety, and insomnia especially among female HCPs during the emergence of COVID-19, prompting psychological preventive measures or interventions (17).

The COVID-19 pandemic put a pressure on all dental healthcare professionals and has affected the delivery of dental health care services globally (13). Today, the mental health and physical well-being of dental professionals has been significantly affected by COVID-19 outbreak in various aspects.

The results showed that, age, work sector, years of experience, having case tracing duty during the COVID-19 pandemic, confidency that being infected with COVID-19 can be avoided during the study, title and gender variables significantly predicted dental healthcare workers' quality of life. Older age, more years of practice, confidency that being infected with COVID-19 can be avoided during the study and being a male heightened psychological and physical resilience while being a research assistant and having case tracing duty during the COVID-19 pandemic lowered psychological resilience.

Global medical human resources are limited. As a result, many hospital-based health care workers have had to work out of hours and take on extra shifts like case tracing. These types of stressors have been associated with poor quality of life (18). Zhao et al. (19) showed that medical staff members in China who had close contact with COVID-19 patients had much higher levels of anxiety and depression when compared with their counterparts who had no contact. Close contact with COVID-19 patients was also shown to negatively affect the medical staff's quality of life (19). Shacham et al. (20) identified psychological distress among dentists and found that the fear of getting infected with COVID-19 from a patient provides high psychological tension. Similarly, in this study, the quality of life of dental professionals who had case tracing duty and had close contact with COVID-19 patients was negatively affected.

Table 4. Evaluation of quality of life according to background characteristics

	Physical aspect Me.±S.D. (median)	Mental aspect Me.±S.D. (median)	SF-36 General Me.±S.D. (median)
Gender			
Male	75.6±15.33 (79.8)	56.08±19.79 (56.5)	65.84±15.95 (67.1)
Female	71.76±17.2 (76)	49.28±20.71 (47.9)	60.52±16.88 (59.8)
p1	0.025*	0.001*	0.001*
Age			
20-29	69.15±15.69 (72)	43.71±18.42 (40.1)	56.43±15.07 (56.4)
30-39	75.5±15.89 (79.8)	50.61±20.02 (50.3)	63.05±16.16 (62.8)
40 and over	74.88±17.61 (82.3)	58.77±20.45 (62.5)	66.83±17.13 (70.8)
p2	0.000*	0.000*	0.000*
Work sector			
Private dental office	75.58±17.16 (82)	55.84±21.71 (59.6)	65.71±17.11 (68.9)
Private dental polyclinic	76.08±13.87 (77)	53.57±20.37 (52.7)	64.82±15.24 (65.5)
Private dental hospital	68.4±18.21 (69.8)	45.35±23.88 (39.8)	56.87±19.58 (60.7)
State university	71.94±16.77 (75.5)	49.35±19.64 (48.3)	60.65±16.85 (61)
Foundation university	69.69±17.01 (75.6)	45.51±17.84 (43)	57.6±14.39 (58.7)
Govermental oral and dental health center	67.65±17.68 (72.8)	48.44±21.3 (44)	58.05±18.11 (57)
Others	53.75±15.66 (50.9)	38.42±8.15 (38.5)	46.09±8.68 (46.1)
	0.000*	0.007*	0.000*
Years of experience			
1-5	68.56±15.81 (70.5)	43.36±17.99 (40)	55.96±14.9 (56.1)
6-10	76.68±14.79 (79.4)	52.16±20.24 (49.2)	64.42±15.21 (62.8)
11-15	75.08±17.21 (82.3)	48.35±21.72 (52.5)	61.72±18.48 (66.1)
16-20	76.43±16.77 (83)	56.59±20.04 (57.2)	66.51±16.66 (70.4)
21-30	73.59±18.2 (80.3)	59.71±19.73 (64.4)	66.65±16.73 (68.8)
30 and over	76.84±16.74 (83.3)	59.98±21.23 (63.8)	68.41±17.75 (73.3)
p2	0.000*	0.000*	0.000*
Title			
Dentists (Dt)	73.27±17.71 (79.8)	54.94±21.18 (58.5)	64.11±17.5 (67.7)
Research assistant (Phd)	69.38±16 (72.8)	43.47±18.23 (40.9)	56.42±14.86 (57)
Specialist	73.84±16.97 (75.6)	52.39±21.2 (52.9)	63.11±17.91 (62.8)
Doctor	78.92±13.16 (82.5)	55.61±22.51 (57.6)	67.26±16.21 (68)
Assistant professors	72.96±17.66 (76.5)	49.41±19.24 (48.6)	61.18±16.69 (63.9)
Associate professor	75.37±15.51 (81.8)	60.4±17.17 (63.3)	67.89±14.38 (65.9)
p2	0.008*	0.000*	0.000*
Speciality			
Oral and Maxillofacial Surgery	73.59±19.54 (84)	51.33±2474 (57.8)	62.46±20.65 (68.5)
Endodontics	77.98±20.88 (87)	48.4±23.71 (38.4)	63.19±18.04 (62.7)
Orthodontics	74.2±21.07 (80.6)	47.2±21.49 (44.2)	60.7±18.25 (61.2)
Periodontology	83.71±8.11 (82.3)	68.67±23.84 (79.8)	76.19±13.56 (76.5)
Prosthetic dentistry	76.63±18.92 (85)	67.25±21.33 (76.8)	71.94±19.85 (82.3)
Restorative dentistry	60.69±23.8 (57.1)	43.5±24.69 (43.8)	52.09±23.26 (46.5)
Pediatric Dentistry	72.75±15.02(75.5)	49.14±19.1 (48.3)	60.94±15.41 (61)
No Specialization/PhD	72.58±18.07(79.4)	54.29±21.79(53.9)	63.44±17.71(65.3)
p2	0.152	0.028*	0.089

[1]Mann Whitney U Test, [2]Kruskal Wallis Test, *p<0.05, Note: Oral and maxillofacial radiology was excluded from the analysis due to low number of participants.

Table 5. Evaluation of quality of life according to work related data

	Physical aspect Me.±S.D. (median)	Mental aspect Me.±S.D. (median)	SF-36 General Me.±S.D. (median)
Contracting the COVID-19 disease			
Yes	70.91±19.92 (77.3)	54.55±21.44 (57.5)	62.73±18.59 (64.3)
No	73.07±16.35 (77.3)	51.16±20.55 (50.1)	62.12±16.61 (61.7)
p1	0.731	0.300	0.717
Emergency patients only			
Yes	71.13±17.03 (75.8)	50.43±18.44 (49.6)	60.78±16.29 (61.1)
No	73.44±16.46 (77.8)	51.48±21.43 (49.9)	62.46±16.89 (62.2)
I do not receive any patients	75.15±21.25 (86)	53.93±17.43 (54.3)	64.54±17.37 (71.1)
p2	0.226	0.868	0.694
Case tracing during COVID-19 pandemic			
Yes	66.94±18.47 (70.4)	45.83±20.08 (43.9)	56.39±17.62 (56)
No	73.53±16.46 (77.8)	51.91±20.65 (52)	62.72±16.59 (62.7)
p1	0.025*	0.065	0.027*
Believing that infection by COVID-19 is a risk to the dentist			
Yes	72.41±17.07 (76.5)	51.23±20.81 (50.2)	61.82±17.05 (61.7)
Partially	78.57±9.95 (81.9)	50.18±16.62 (47.3)	64.38±11.04 (62.5)
p1	0.133	0.774	0.514
Confidency that being infected with COVID-19 can be avoided during the study			
I am not confident	70.25±18.03 (74.5)	48.73±19.65 (48)	59.49±16.93 (59.7)
I am confident enough	78.05±13.18 (81.4)	57.77±20.76 (61.9)	67.91±14.73 (69.3)
I'm a little confident	73.74±14.72 (75.1)	50.61±19.63 (49.9)	62.18±15.23 (62.4)
I think I can be protected with the vaccine	83.71±13.21 (88)	67.73±20.97 (76.4)	75.72±15.33 (80.6)
p2	0.000*	0.000*	0.000*

[1]Mann Whitney U Test, [2]Kruskal Wallis Test, *p<0.05, Note: The answer "No" for the question of believing that infection by COVID-19 is a risk to the dentist, excluded from analysis due to paucity.

The findings of this survey suggest that almost all the dentists were experiencing some form of mental health symptoms and stress because of changes in their daily work routine due to the pandemic situation in Turkey. In a previous study in the UK, statistically significant associations between the mental health and stress levels of dentists were discovered due to work-related changes implemented to reduce the transmission of the virus during the peak of the pandemic (21). In the letter study, dentists who were not working had more anxiety and depressive symptoms compared with the working group. Although both places of work (independent and public sector) had a statistically significant risk of poor MH, dentists working in the public sector were less affected and had reduced odds of developing MH symptoms (21). In the study conucted with healthcare workers, Aşkın Ceran et al., revealed no statistically significant difference between the SF-36 scale mean scores according to the work sector of dental professionals' work during the COVID-19 pandemic (22). Unlike, the study carried out by Aşkın Ceran et al., in this study, it was found that dentists in the private dental office had statistically significant mental health scores compared with those in the public sector. This could be attributed to the large number of dental patients visiting the public centers per day in comparison to private clinics (23). Working in an independent sector seemed to have a protective effect for quality of life. Morever, in this study, no significant difference was found between life quality and mental health scores of dental professionals who examined all of the patients, those who examined only emergency patients and those who did not examine any patients.

It was found that socio-demographic characteristics of dental professionals such as age and gender affected SF-36 scores in this study. The SF-36 scale mean score and, mental and physical health scores of male participants were significantly higher than those of female patients. Unlike our research findings, in a study conducted by Su etal. in Taiwan, no statistically significant difference was observed between the SF-36 scale mean scores of female and male participants (p=0.21) (24). Also, Aşkın Ceran et al., reported that there was no statistically significant difference between the SF-36 scale mean scores according to gender (22).

Dental professionals' work experience had an impact on instability, infection and concerns. Dental professionals with longer working experience were less likely to report fear of changes in the work-environment (heavy workload), fear of being infected and infecting (13). On the other hand, to the results of this study, we found that dental professionals with the shortest working experience (1-5 years) had the lowest SF-36 mean for mental and physical health scores.

In addition, it was observed that there was no statistically significant difference between the SF-36 scale mean scores of those who were infected with COVID-19 and not infected with COVID-19 during the pandemic ($p>0.05$). It was revealed that contracting the COVID-19 disease did not affect the SF-36 scale mean scores.

Limitations

The study has certain limitations. First of all, this study was based on a cross-sectional observation survey. We also do not know whether this lower quality of life existed before COVID-19. Similarly, online self-assessment questionnaires may be affected by the difficulty of completing them. This could affect the validity of the data provided.

CONCLUSION

The present study showed a considerable psychological impact of the COVID-19 pandemic on dental professionals in Turkey regardless of working clinically with patients or not. Promoting the mental health and life quality of all dental professionals should be a critical part of the public health response, and specific efforts should be directed to sensitive sectors. Dental professionals must take measures to make this unending experience as bearable as possible, and public health officials must act cautiously and be more attentive to sectors that seem to have been forgotten. Strategies to prevent and support the stressed dentists will help the dental profession in the long term.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpaşa Training and Research Hospital, Medical Researchs Local Ethics Committee (Date: 17.03.2021, Decision No: 2021-243).

Informed Consent: The electronic informed consent was obtained if the participants agreed to complete the questionnaire.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Comparison of open repair and modified percutaneous repair techniques for the treatment of acute Achilles tendon ruptures

Lokman Kehribar[1], Hüseyin Sina Coşkun[2], Serkan Sürücü[3]

[1]Samsun University, Faculty of Medicine, Department of Orthopedics and Traumatology, Samsun, Turkey
[2]Ondokuz Mayıs University Faculty of Medicine, Department of Orthopedics and Traumatology, Samsun, Turkey
[3]University of Missouri Kansas City, Department of Orthopaedic Surgery, USA

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ABSTRACT

Background: This study compared acute Achilles tendon repairs' functional and clinical outcomes with two different surgical techniques; modified percutaneous and open repair.

Material and Method: This retrospective study analyzed 57 patients with an acute Achilles tendon rupture (AATR) who underwent modified percutaneous and open repair. 46 patients who met the eligibility criteria were enrolled and divided into two groups based on the surgical technique. 23 patients from Group 1 were treated using modified percutaneous repair under local anesthesia, and 23 patients from Group 2 were treated with an open repair under regional anesthesia. Postoperatively, patients were evaluated using American Orthopedic Foot and Ankle Society (AOFAS) Hindfoot Questionnaire score at final follow-up. The other outcomes included return to work, return to sports activities, capacity to complete single heel rise, leg circumference, estimated limb symmetry indices, Achilles tendon resting angle (ATRA), complications, and timing of index surgery.

Results: At the time of surgery, the mean age of the patients was 35.9 7.5 years (range, 25–47 years). The average follow-up was 34.8±6.5 months (24–52 months). The mean age, gender, body mass index (BMI), rupture level, duration from injury to surgery, and mean follow-up time were similar in both groups. At a minimum 2-year follow-up, good pain relief was achieved for all patients. The AOFAS scores were 93.4±4.1 (88-100) in Group 1 and 92.2±5.2 (82-100) in Group 2. There was no statistically significant difference between groups concerning the Achilles tendon resting angle (ATRA), calf circumference, single-leg heel rise, return to work, and return to sports activities. However, the percutaneous repair procedure had a shorter surgical time than the open repair technique ($p<0.05$).

Conclusion: Modified percutaneous and open repair techniques provide similar clinical and functional outcomes, but the percutaneous repair technique showed faster surgical time than open procedures. Furthermore, the percutaneous technique may be more practical than the open technique, which may be performed under local anesthesia.

Keywords: Achilles tendon, rupture, repair, percutaneous

INTRODUCTION

Despite advancements in treatment and rehabilitation, the ideal management of acute Achilles tendon rupture (AATR) continues to be debated (1). Several treatment options have been recommended, including immediate immobilization, open repair, percutaneous repair, and functional rehabilitation (2-4). Conventionally, the open repair was favored secondary to its lower re-rupture rates, however in more recent years, and there has been a progressive shift away from surgical intervention to reduce wound complications (5,6). On the other hand, conservative options have been shown to carry an increased rate of re-rupture and tendon lengthening and other long-term complications (7,8). Percutaneous repair has been criticized for healing in a lengthened tendon position and exposing the sural nerve to a significant risk of injury (9-11). Currently, there is no decision on the best method to be used, with advantages and disadvantages for all options.

Recently, meta-analyses showed that the percutaneous techniques promoted faster surgical time, lower rate of wound complications, and a similar re-rupture risk compared to an open repair (6,12). Many surgeons advocate for open repair despite improved percutaneous techniques because of reliable anatomical tendon repair with direct visualization and lower re-rupture risk (13,14). There is still disagreement over which method is more effective: open or percutaneous.

Corresponding Author: Hüseyin Sina Coşkun, sina.coskun@hotmail.com
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This study aimed to assess the functional and clinical outcomes of modified percutaneous and open Achilles tendon repairs. We hypothesized that a modified percutaneous technique with a sliding knot using absorbable sutures would have clinical outcomes comparable to an open repair technique.

MATERIAL AND METHOD

The study was carried out with the permission of Ondokuz Mayıs University Clinical Researchs Ethics Committee (Date: 23.09.2021, Decision No: 2021/424). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective analysis comprised 57 individuals who had an acute Achilles tendon rupture (AATR) and underwent modified percutaneous and open repair. All of the ruptures were occurred during a sporting activity, mainly while running or playing football. The inclusion criteria were as follows: (1) patients with an AATR time from injury of less than ten days; (2) age range of 18-60 years; (3) no history of ankle pathology; and (4) no significant comorbidities. Eleven patients were excluded from the study because of rheumatoid arthritis (n=1), immunodeficiency (n=1), less than 24 months follow-up (n=5), and chronic rupture (n = 4). 46 patients who met the criteria were enrolled and divided into two groups based on the surgical technique. Group 1 comprised 23 patients who were treated with a modified percutaneous repair. Group 2 was comprised of 23 patients who were treated with an open repair.

Physical and Clinical Assessment

All patients underwent a full physical examination preoperatively, including an ankle range of motion test, the Thompson test, and a gap palpation test. Patients were evaluated using the American Orthopedic Foot and Ankle Society (AOFAS) Hindfoot Questionnaire score at the final follow-up. Additionally, the ability to perform single heel rises, leg circumference, calculated limb symmetry indexes, Achilles tendon resting angle (ATRA), complications, and timing of surgery were evaluated.

Surgical Technique

All patients were positioned prone without the use of a tourniquet. The study's senior author carried out all procedures.

In Group 1, modified percutaneous repair with a sliding knot using absorbable suture was performed under local anesthesia. Tendon gaps and stumps were identified, and three pairs of stab incisions were made at each ruptured tendon end. Tendon ends were sutured according to Bunnell type repair, and the suture ends were pulled to tighten at the level of the middle medial stab incision. A non-locking loop was created using a sliding knot by pulling the post strand. The length of the repaired tendon was estimated by measuring the Achilles' resting angle of the contralateral foot. The palpable gap disappeared, and finally, the incisions were closed with absorbable sutures (**Figure 1**).

In group 2, the open repair was performed under spinal anesthesia. A posteromedial approach was used to access the Achilles tendon. Ruptured tendon fascicles were adapted and sutured with modified Kessler type repair using absorbable suture (No:1 PDS). Further continuous sutures were applied to encircle the fascicles. The paratenon and fascia were then thoroughly repaired. Finally, the wound was closed with an absorbable suture.

Postoperative Rehabilitation

Each group followed a similar postoperative rehabilitation protocol. A short leg cast was applied with the ankle for two weeks in 20° of equinus. The cast was changed after soft tissue healing with a second cast set at a 10° plantarflexion angle for two weeks. During this period, muscle strengthening exercises were recommended with partial weight-bearing. After four weeks, patients were instructed to walk with weight-bearing and perform isokinetic and isometric strengthening exercises.

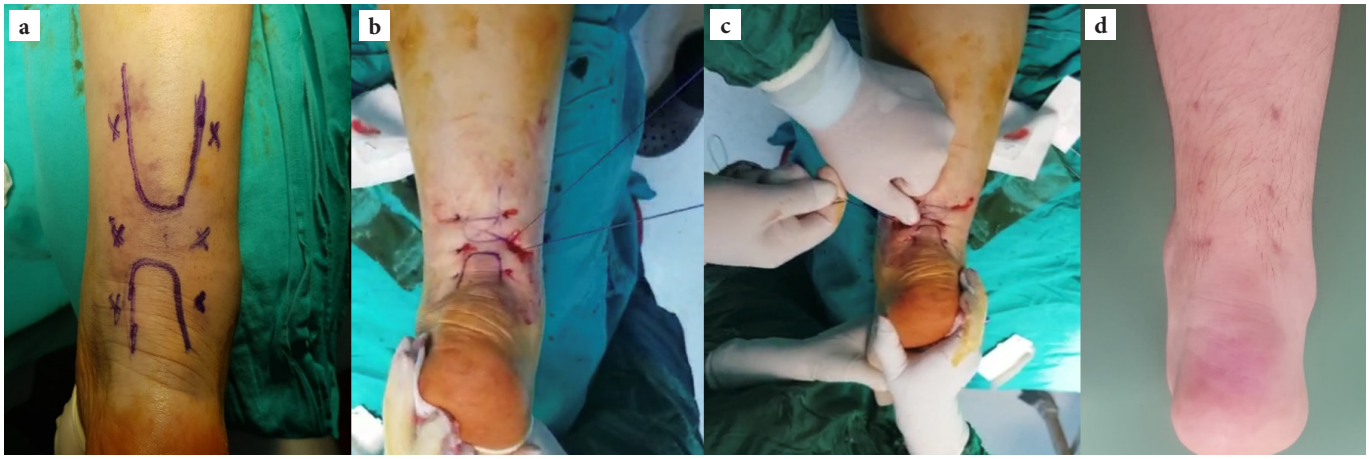

Figure. **a)** Marking the skin for the suture pass points. Note the gap where the rupture occurred **b)** and **c)** Thightening the suture on the medial side of the foot and using it as a gliding suture. **d)** Completely healed wound after three months postoperatively.

Statistical Analysis

Power analysis has been done for the study. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) Version 21.0 statistical analysis software. The Shapiro-Wilk test defined normal distribution. The postoperative comparisons were performed using the Student t-test as quantitative data. The quantitative data were shown as the mean±standard deviation. The sample size was determined using a power analysis, which found that at least 20 patients were required for each group to achieve a minimum power of 80% with a 5% alpha error.

RESULTS

This study enrolled 46 patients (33 males and 13 females). At the time of surgery, the mean age of the patients was 35.9±7.5 years (range, 25–47 years). The average follow-up was 34.8±6.5 months (24–52 months). The mean age, gender, body mass index (BMI), rupture level, duration from injury to surgery, and mean follow-up time were similar in both groups. Detailed comparative demographics in both groups are shown in **Table 1**.

Table 1. Patient demographics

	Mean±SD (Range)		P value
	Group 1 (n=23)	Group 2 (n=23)	
Age	37.5±6.1 (28-47)	34.6±5.5 (25-42)	0.625
Sex (M/F)	17/6	16/7	0.562
BMI (kg/m2)	26.6±3.4 (21-32)	25.3±4.5 (22-34)	0.821
Side (R/L)	12/14	12/11	0.235
Level of rupture (cm)	5.6±1.2 (4.5-6.5)	5.1±2.3 (4-6.5)	0.461
Time from injury to surgery (days)	3.1±1.7 (1-8)	2.5±2.1 (0-9)	0.523
Follow-up (months)	33.2±7.2 (24-46)	35.1±7.8 (24-52)	0.341

Group 1: Modified percutaneous repair; Group 2: Open repair; BMI: body mass index; M: male; F: female; R: right; L: left; SD: standard deviation

At a minimum two-year follow-up, all patients achieved significant pain relief. The functional outcomes were similar in both groups. The AOFAS scores were 93.4±4.1 (88-100) in Group 1 and 92.2±5.2 (82-100) in Group 2. There was no statistically significant difference between groups concerning the Achilles tendon resting angle (ATRA), calf circumference, single-leg heel raise, return to work, return to sports. The indexes of limb symmetry for an ATRA, calf circumference, and single-leg heel rise were not significantly different. However, the percutaneous repair procedure was found to have a much shorter surgical duration than the open repair technique ($p<0.05$). **Table 2** summarizes the statistical comparisons between the two groups.

Table 2. The comparison of clinical and functional outcomes of groups

	Mean± SD (Range)		P value
	Group 1 (n=23)	Group 2 (n=23)	
AOFAS score	93.4±4.1 (88-100)	92.2±5.2 (82-100)	0.118
ATRA (degree)	55.4±6.2 (45–74)	54.1±5.3 (42–76)	0.234
ATRA LS index (%)	102.5±6.8 (95–130)	101.3±5.4 (90–135)	0.315
Calf circumference (cm)	38.4±7.1 (28–49)	34.6±6.4 (24–43)	0.254
Calf circumference LS index (%)	95.4±5.6 (88–103)	92.6±5.2 (85–104)	0.556
Single leg heel raise (count)	39.5±8.3 (27–96)	38.2±7.4 (26–95)	0.343
Single leg heel raise LS index (%)	84.6±10.1 (52–115)	82.1±8.6 (50–110)	0.253
Return to work (day)	41.3±6.7 (32–58)	46.8±5.6 (36–60)	0.152
Return to sports (month)	4.5±1.2 (3–6)	4.8±1.5 (3–8)	0.142
Operation duration (min)	14.4±3.2 (10–23)	32.6±6.1 (25–44)	0.001

Group 1: Modified percutaneous repair; Group 2: Open repair; AOFAS: American Orthopaedic Foot Ankle Society Rating Score; ATRA: Achilles tendon resting angle; LS Index: Limb symmetry index= affected limb side/healthy limb side * 100 %; SD: standard deviation; *p<0.05 statistically significant

Temporarily sural nerve damage was found in 2 patients in Group 1. Two patients had developed superficial wound infections in Group 2.

DISCUSSION

The percutaneous technique was first described in 1977 by Ma and Griffith (15). Since then, this procedure has gained wide acceptance as a treatment option with satisfactory outcomes to minimize the wound complications related to the open procedure. However, this technique was criticized for re-ruptures based on inadequate suturing due to no visualization of the tendon (3,8). Also, this approach was more prone to sural nerve injury and tendon elongation. However, surgical techniques have continued to evolve. Initially, a sural nerve palsy rate of up to 60% has been reported, whereas the most recent studies reported the occurrence rate was 5.5% (16). Nowadays, studies reveal the anatomy more detailed than before, so thanks to this, we can safely perform the percutaneous repair (17). In our study, the temporary sural nerve damage was found in two patients in the percutaneous group.

Although percutaneous AATR surgery has gained favor, some surgeons advocate for open repair due to biomechanical strength issues (18). Because of the direct visualization of the ruptured tendon, the authors believe that the incidence rate of re-rupture may decrease. However, previously conducted meta-analyses suggested

no significant difference in the re-rupture rate between the percutaneously and open techniques (12,19). On the other hand, wound healing problems with deep infection continue to be a concern. The deep infection rate has been reported to reach up to 20% (20). In our study, two patients had developed superficial wound infections in the open repair group.

In their meta-analysis, Yang et al. (12) suggested that percutaneous repair is superior to open repair for treating AATR. They reported that the percutaneous technique has several advantages, including operation duration, lower rate of deep infection, and higher AOFAS score. Similarly, Makulavicius et al. (3) reported that both percutaneous and open repair procedures were effective, safe, and resulted in a high level of patient satisfaction. Furthermore, they showed that the percutaneous technique was significantly faster than the open technique. Likewise, in our study, the surgical duration of the percutaneous repair was found significantly lower than an open repair technique. Also, the percutaneous repair was performed under local anesthesia in all patients. However, the open repair was required regional anesthesia.

Achilles tendon elongation after surgery and adjustment of the tendon length are the major concerns for surgeons in percutaneous techniques (11,21). Several studies showed that the plantar flexion strength and single-leg heel raise endurance decreased after Achilles tendon elongation (10,22). These findings reiterated skepticism about the dilemma for open or percutaneous repair techniques. Clanton et al. (13) found that the percutaneous repair techniques demonstrated significantly early elongation than open repair techniques. They reported that the primary elongation mechanism resulted from cut-out at the suture-tendon interface and knot slipping or stretching. Our study suggested the modified percutaneous technique with a sliding knot to reduce the knot-related complications causing the tendon elongation. The superiority of the presented modified method consists of non-locking and sliding knot mechanisms. It maintains the restoration of the original tendon length and provides good tendon healing without elongation.

Furthermore, it allows the repair of the ruptured tendon in similar tension with the contralateral side. Intraoperatively, tightness of tendon repair was quantified using the contralateral ATRA. At the final follow-up, there was no statistically significant difference between open and percutaneous techniques concerning the ATRA limb symmetry index.

The study's main significant finding was that open and modified percutaneous repair procedures are equally effective, yielding "excellent and good" clinical outcomes following AATR. Furthermore, compared to open repair, the percutaneous technique had a much shorter surgery duration. The percutaneous Achilles tendon repair has a higher risk of sural nerve damage but a lesser risk of wound complications/infection than open repair.

Our study noted that there were no significant difference in terms of returning to work and sport. We expected an earlier return in the percutaneous group. Still, we concluded that return to work and sporting activity is a subjective factor depending on the patient's pre-injury activity level and many other factors. This part needs to be clarified in light of future studies. It is critical to resume previous activities. Both time and pre-injury level recovery need to be considered. Although the rate of sports discontinuation is up to 8.6 % following percutaneous repair, 78% of athletes returned to their previous activity level (23).

The study had several limitations. The major limitation of this study was its retrospective design and small sample size. In addition, muscle strength and endurance were not evaluated with a specialized device. Further researches are needed to make precise conclusions on this subject.

CONCLUSION

Modified percutaneous and open repair techniques provide similar clinical and functional outcomes. But, the percutaneous repair technique showed faster surgical duration than the open technique. Furthermore, the percutaneous technique may be practical because it may be performed under local anesthesia.

ETHICAL DECLARATIONS

Ethical Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researchs Ethics Committee (Date: 23.09.2021, Decision No: 2021/424).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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Author Contributions: All of the authors declare that they have all participated in the paper's design, execution, and analysis and that they have approved the final version.

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Original Article

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The difference between the cycloplegic and noncycloplegic refractive error may be an indicator for the myopia progression in myopic children

Sücattin İlker Kocamış[1], İbrahim Özdemir[2]

[1]Yenikent State Hospital, Ophthalmology Department, Sakarya, Turkey
[2]Dünyagöz Hospital, Ophthalmology Department, Sakarya, Turkey

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ABSTRACT

Aim: We aimed to evaluate the relationship between the subjective and objective refractive error measurement difference and myopia progression in this study.

Material and Method: Children between 6-18 year-old at the beginning of the follow-up period having myopia and who were followed up regularly every six months and for a total of at least 36 months were included in the study. All children underwent a detailed ophthalmologic examination. An autorefractor (TOPCON KR1/RM1, Topcon, Oakland, New Jersey), was used to evaluate the refractive error. Those with a refractive error difference of less than 0.50 D (spherical equivalent) before and after cycloplegia were included in group 1. Those with a refractive error difference of higher than 0.50 D were included in group 2. Myopic progression of the groups was compared.

Results: This study comprised 44 patients (male, 23; female, 21) in group 1 and 42 patients (male, 22; female, 20) in group 2. The age range and mean age±SD of patients in group 1 were 6-17 years and 11.4±3.0 years, respectively, whereas that of patients in group 2 was 6-17 years and 12.6±3.3 years, respectively. Both groups were followed for similar periods (p= 0.141). It was 37.5±2.4 (range 36-48) months in group 1 and 36.8±1.6 (range 36-42) months in group 2. The range and mean of the cycloplegic refractive error at the beginning of the following period in group 1 were -2.37±1.15 D, and -1.75±0.99 D in group 2 respectively (p= 0.010). At the end of the following period, the mean cycloplegic refractive error were -2.73±1.11 D in group 1, and -3,33±0.91 D in group 2 respectively (p= 0.008). During follow-up, the change in cycloplegic refractive error was 0.36±0.16 D in group 1, and 1.57±0.46 D in group 2. It was significantly lower in group 1 than group 2 (p< 0.0001).

Conclusion: We demonstrated that myopic children having high baseline difference between the objective and subjective spheric equivalent measurements had more myopia progression.

Keywords: Accommodation, cycloplegic refraction, myopia progression

INTRODUCTION

Myopia is one of the main causes of childhood blindness (1). Research on myopia is gaining more attention as it has become a worldwide public health issue. Although mild to moderate myopia is usually innocuous, high myopia may lead to significant ocular morbidities like cataract, retinal detachment, macular hole, and glaucoma (2). Therefore, understanding the pathophysiology of myopia progression is a significant issue. Risk factors for myopia progression are still unclear. Nevertheless genetics, ethnicity, age and near work are the mostly emphasized factors in myopia progression (3-6).

Excessive accommodation and ciliary muscle spasms due to the sustained near work lead to the alteration of the lens and myopic defocus on the retina subsequently. In the Tehran eye study, it was found that the difference between the objective and subjective refractive error was up to 0.71 Diopter (D) in 5-10 years children (7). According to the Chinese Medical Association of Ophthalmology, accommodative factors are taking part in %60 of the myopic school aged children (8). Therefore, accommodative incongruences might be a research issue for myopia progression.

Corresponding Author: Sücattin İlker Kocamış, drilkerkocamis@gmail.com
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Cycloplegic refraction should be employed especially in children while detecting the exact refractive error. Cycloplegia eliminates the accommodation and prevents the overestimation of myopia (9). Pseudo myopia is defined as high myopia due to the accommodative spasm which caused by the prolonged near work. After cycloplegia, myopia is disappeared in pseudo myopia. Despite that, myopia still exists and is not decreased more than 0.50 D in true myopia (8). In our clinic, we observe patients with more than 0.50 D myopia decrease and still having myopia after cycloplegic refraction. Accordingly, we aimed to evaluate the relationship between the subjective and objective refractive error measurement difference (SOD) and myopia progression in this study.

MATERIAL AND METHOD

This study was planned retrospectively to review patients who came to the ophthalmology department with the complaint of farsightedness or diagnosis of myopia between December 1, 2016 and to March 30, 2021. This study was approved by the Ethics Committee of the Sakarya University Medical School (Date: 25.10.2021, Decision No:74730), and all procedures were performed adhered to the ethical rules and principals of the Helsinki Declaration.

Children between 6-18 year-old at the beginning of the follow-up period having myopia and who were followed up regularly every six months and for a total of at least 36 months were included in the study. The exclusion criteria were as follows: strabismus, best- corrected visual acuity <10/10, astigmatism > 1.00 D in either eye, anisometropia of >1.0 D between the two eyes, any ocular disorders which may contribute to refractive error change such as cataract and keratoconus, and the usage of any methods to prevent myopia progression.

All children underwent a detailed ophthalmologic examination. Visual acuity with and without correction was tested using Snellen chart. The children were examined monocularly (right eye followed by left eye). A cover test was used to check for the presence of strabismus. For each child, a drop of topical anesthetic (ALCAINE; Alcon Laboratories, TX, USA), and then two drops of 1% cyclopentolate (SIKLOPLEJIN; Abdi Ibrahim, Ist, Turkey) were applied at five-minute intervals. Thirty minutes after the last drop, a third drop of cyclopentolate was administered if the pupillary light reflex was still present. An autorefractor (TOPCON KR1/RM1, Topcon, Oakland, New Jersey), was used to evaluate the cycloplegic refractive error.

Those with a refractive error difference of less than 0.50 D (spherical equivalent) before and after cycloplegia were included in group 1. Those with a refractive error difference of higher than 0.50 D were included in group 2. Myopic progression of the groups was compared.

Data were statistically analyzed using the statistical package for social sciences package v.25.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess the normal distribution and Levene's test was used to assess variance homogeneity. Independent Sample T Test, Paired Sample T Test and Chi Square Test were also used to evaluate the significant differences between the groups. The value of statistical significance was set at P 0.05

RESULTS

This study comprised 44 patients (male, 23; female, 21) in group 1 and 42 patients (male, 22; female, 20) in group 2. The mean age±SD of patients in group 1 was 11.4±3.0 years (range 6-17 years), whereas that of patients in group 2 was 12.6±3.3 years (range 6-17 years) (p=0.069) (p=0.069). Both groups were followed for similar periods (p= 0.141). It was 37.5±2.4 (range 36-48) months in group 1 and 36.8±1.6 (range 36-42) months in group 2 (**Table 1**).

The range and mean of the cycloplegic refractive error at the beginning of the following period (T0) in group 1 were -2.37±1.15 D, and -1.75±0.99 D in group 2 respectively (p= 0.010). At the end of the following period (T1), the mean cycloplegic refractive error were -2.73±1.11 D in group 1, and -3,33±0.91 D in group 2 respectively (p= 0.008). During follow-up, the change in cycloplegic refractive error was 0.36±0.16 D in group 1, and 1.57±0.46 D in group 2. It was significantly lower in group 1 than group 2 (p< 0.0001) (**Table 1**).

Table 1. Demographics of groups and distribution of variables by group

	Group1 n=44	Group2 n=41	P value
Sex F/M	23/21	22/20	0.992
Age, year	11.4±3.0	12.6±3.3	0.069
Period, month	37.5±2.4	36.8±1.6	0.141
T0, D	-2.37±1.15	-1.75±0.99	0.010
T1, D	-2.73±1.11	-3,33±0.91	0.008
ΔT, D	0.36±0.16	1.57± 0.46	<0.0001

D: Diopter, F: Female M: Male, T0: the cycloplegic refractive error at the beginning of the following period, T1: the cycloplegic refractive error at the end of the following period, ΔT: the change in cycloplegic refractive error

DISCUSSION

In this study, we found that myopic children having greater amounts of SOD initially were more prone to myopia progression. This finding is also in agreement with the outcome of a research derived from the Beijing Myopia Progression Study (10). This study enrolled two hundred and nineteen children aged 6-17 with three years follow up time. It was stated that baseline SOD was correlated with the myopia progression but not associated with onset of myopia. We think that the

result of our study is important regarding that it can be employed as a useful method to determine the specific patient population that needs treatment in order to prevent myopia progression.

The possible relationship between the accommodation and myopia has been extensively discussed for a long time. In animal models, it was demonstrated that administration of minus lenses provoked the elongation of the eye and myopia (11,12). Based on these studies, it was claimed that insufficient accommodation response to the accommodative stimuli, lag of accommodation, may lead to the hyperopic blur on the retina and cause axial elongation eventually (13,14). Thus, undercorrection of myopia was suggested as a solution to halt the progression. However, it was claimed that undercorrection had no effect on slowing the progression (15). Moreover, some studies showed that undercorrected children had more myopia progression than the fully corrected children (16,17). Undercorrection induces myopic defocus like excessive accommodation does. Therefore, we think that myopic defocus due to excessive accommodation may lead to the myopic progression in our study. Moreover, Jin et al.'s (18) recent study showed that SOD is negatively correlated with the accommodation lag. Based on this study, we can state that myopia progression in our study cohort is not associated with the high accommodation lag. Additionally, in Hussaindeen et al. (19) study, it was demonstrated that in myopic eyes having more than 1D difference in SOD, all of the accommodation factors other than the accommodation amplitude were not significantly different than the control group.

There are numerous works indicating the possible relation between the near work and the myopia progression, thus supporting the potential role of accommodation in myopia progression (20,21). Nevertheless, attempts to modify the accommodation and slowing the myopia progression with undercorrection, bifocal and multifocal spectacles seem to have mild and clinically nonsignificant outcomes (22). In a clinical study, bifocal soft contact lenses and spherical soft contact lenses were employed in the contralateral eyes of the myopic children simultaneously. After a certain period, the lenses were switched and used for the same amount of time. It was demonstrated that bifocal contact lenses slowed myopia progression much more compared to soft spherical lenses even after the switching (23). This study indicated that peripheral myopic defocus might be the notable factor rather than the accommodation in myopia progression as the accommodation was modified evenly in both eyes. Also, it was shown that despite the intensity of the near work increases with the age, the myopia does not progress (24).

It was proposed that accommodation errors might be a consequence of myopia rather than the reason of it (25). The amount of SOD was gradually decreased in high SOD group after the full correction with spectacles throughout the follow up in the Lin et al. (10) aforementioned study. Therefore, we can assert that excessive accommodation might be induced due to the uncorrection of myopia during certain amount of time. However, in our study, we do not exactly know since when they had been myopic before the treatment. Another significant agent administered in myopia progression is atropine. Based on the animal studies, it is thought that atropine does not slow the myopia via reducing the accommodation (26). However, the exact mechanism is still unknown. We think that adopting the animal models exactly into human pathophysiology may cause bias. We cannot fully exclude the role of accommodation mechanism according to the fact that rebound effect is seen after the cessation of the atropine (27). Accordingly, we suggest the administration of atropine to the myopic patients having initial SOD more than 0.50 D and progressive myopia in order to benefit from both cycloplegic effect and neuromodulator effect of the atropine to halt the myopia progression.

Our study has some drawbacks mostly arises from the nature of retrospective design. Firstly, our sample size was relatively small. Secondly, axial length measurements were absent. However, initial cycloplegic refractive error was higher in low SOD group than the high SOD group. It was suggested that higher initial myopic error would lead to more myopia progression (28). Therefore, the results in this study reinforce our hypothesis. Nonetheless, comparing the differences in axial lengths in both groups would contribute to myopia progression evaluation. Thirdly, no data about the near work activities were present. On the other hand, all the children were school aged children. Lastly, it is known that higher order aberrations can have effect on the measured SOD (29). Corneal aberrations were not measured in our study cohort. However, it was presented that there was no statistically significant difference in aberrations between the myopic eyes having high SOD and having normal SOD (18).

CONCLUSION

In conclusion, we demonstrated that myopic children having high baseline difference between the objective and subjective spheric equivalent measurements had more myopia progression. Further prospective studies with larger sample sizes are needed to investigate whether this difference is a consequence of untreated myopic error for a certain amount of time and its possible relation with the myopia progression.

ETHICAL DECLERATIONS

Ethics Committee Approval: The study was initiated with the approval of the Sakarya University Medical School Ethics Committee (Date: 25.10.2021, Decision No:74730).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Tp-e interval and Tp-e/JT ratio before and after catheter ablation in patients with Wolff Parkinson White syndrome

Ahmet Akdi[1], Özcan Özeke[2]

[1]Ankara City Hospital, Department of Cardiology, Ankara, Turkey
[2]University of Health Sciences, Ankara City Hospital, Department of Cardiology, Ankara, Turkey

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ABSTRACT

Aim: Tp-e and Tp-e/QT are novel markers of ventricular repolarization. However, preexcitation in Wolff Parkinson White (WPW) syndrome may preclude accurate measurement of repolarization as assessed by the QT. We aimed to research the assessment of Tp-e and Tp-e/JT before and after ablation in WPW.

Material and Method: We enrolled 50 consecutive patients with symptomatic WPW syndrome who underwent catheter ablation of their accessory pathways for treatment. All of the patients were successfully ablated. ECGs were performed before the procedure and repeated after the ablation procedure.

Results: Tp-e (86.6±16.2 vs 80.6±12.5; p=0.021) and Tp-e(c) (96.7±18.9 vs 88.3±11.2; p=0,005) showed a significant decrease after the procedure. Tp-e/JT (0.307±0.053 vs 0.279±0.040; p=0.001) and Tp-e/JT(c) (0.276±0.048 vs 0.255±0.045; p=0.009) showed a significant decrease after the procedure. There was a significant association between ERP and before procedure Tp-e (c) (r=- 0.370, p=0.008) and Tp-e/JT (r=- 0.371, p=0.008).

Conclusion: This study demonstrated that Tp-e and Tp-e/JT were significantly diminished in WPW after the ablation.

Keywords: Catheter ablation, JT interval, Tp-e interval, Tp-e/JT ratio, Wolff Parkinson White syndrome

INTRODUCTION

The Wolff-Parkinson-White (WPW) syndrome means to the presence of an overt accessory atrioventricular pathway, in combination with usually recurrent tachyarrhythmias, which may provoke ventricular tachyarrhythmias (VT) (1). In patients with WPW syndrome, the propagating impulse is conducted over the accessory pathway and causes ventricular preexcitation leading to typical alterations of ventricular depolarization and repolarization. Delayed ventricular repolarization has also been associated with VT (2).

Ventricular repolarization can be defined on ECG using QT interval, QT dispersion, and T-wave measurements. The QT interval represents both ventricular depolarization and repolarization, so it is dependent on the QRS duration. Several studies have shown that the Tp-e interval, the interval between the peak and the end of the T wave, is specified as an index of total dispersion of repolarization (3-5). Longer Tp-e interval may predict ventricular arrhythmias and mortality (6,7). Therefore, the Tp-e/QT ratio was suggested to be a better marker of ventricular arrhythmias (8,9).

Depolarization abnormalities in WPW patients may preclude accurate measurement of repolarization as assessed by the QT and corrected QT intervals. The JT and corrected JT (JT(c)) intervals particularly represent ventricular repolarization and have been shown to be independent of the ventricular depolarization and the QRS duration (10). Instead of the QT interval, the JT interval may be a more reliable measure of repolarization in WPW syndrome due to ventricular activation abnormalities. In this study, we aimed to research the assessment of Tp-e interval and Tp-e/JT ratio before and after catheter ablation in patients with WPW syndrome.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital, Clinical Researchs Ethics Committee (Date: 2021, Decision No: E1-12-2031). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Corresponding Author: Ahmet Akdi, 17akdi@gmail.com
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Study Population

In this study, we retrospectively enrolled 50 consecutive patients with symptomatic WPW syndrome who underwent catheter ablation of their accessory pathways for treatment. All of the patients were successfully ablated. Patients who have either an atrial fibrillation/flutter, or permanent pacemaker therapy, or a complete/incomplete bundle branch block were excluded.

Catheter Ablation Procedure

Prior to the procedure, all antiarrhythmic agents were withdrawn at least five half-lives. After vascular access was gained via femoral veins, two diagnostic catheters were placed in the right ventricle and coronary sinus for the electrophysiological study. Programmed atrial and ventricular stimulation was performed to induce atrioventricular reentrant tachycardia and to measure the effective refractory period (ERP) of the accessory pathway. In patients with left-sided pathways, a transseptal puncture was performed to access the left atrium. The ablation catheters were navigated under fluoroscopic and electroanatomic system guidance (Carto 3, Johnson and Johnson, USA). Programmed atrial and ventricular stimulation was performed to confirm the diagnosis of WPW, induce atrioventricular reentrant tachycardia, and prove the presence of an additional pathway, as well as to localize the exact location of the accessory pathways, as described in the literature (11). Directly before ablation, the bundle signal was marked using an ablation catheter on a three-dimensional (3D) map. Irrigated tip ablation was used while delivering radiofrequency energy. The catheter ablation was defined as a success when provided no signs of arrhythmia were documented within 15 minutes after the procedure.

Electrocardiography

The 12-lead ECG was recorded at a paper speed of 50 mm/s (Hewlett Packard, Page-writer, CA, USA) in the supine position. ECGs were performed before the procedure and repeated again after the ablation procedure. ECG measurements of JT and Tp-e intervals were performed by two cardiologists who were blinded to the patient data. An average value of three readings was calculated for each lead. All measurements were made manually from the same lead (**Figure 1**). The QT interval was measured from the beginning of the QRS complex to the end of the T wave and the JT interval was measured from the endpoint (J point) of the QRS complex to the end of the T wave. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. The QT, the JT and the Tp-e intervals were corrected for the heart rate using the Bazett formula: $QT(c)=QT\sqrt{(R\text{-}R\ interval)}$. The Tp-e/JT, the Tp-e/QT, the Tp-e/JT(c), the Tp-e/QT(c) ratios were calculated from these measurements.

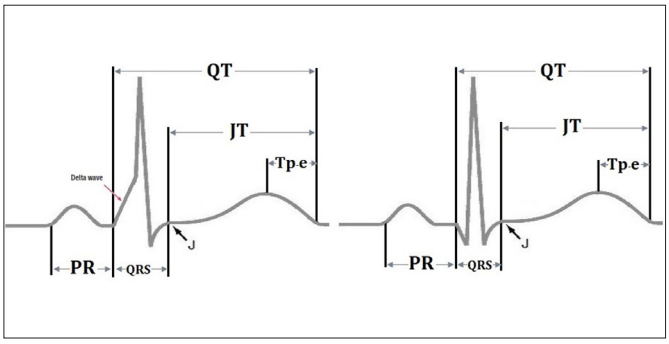

Figure 1. ECG measurements were made from the same lead as in the figure before and after catheter ablation.

Statistical Analysis

For statistical analysis, SPSS 22.0 Statistical Package Program for Windows (SPSS, Inc., IL, USA) was used. In order to test the normality of distribution Kolmogorov-Smirnov test was used. Quantitative variables with a normal distribution were specified as the mean±standard deviation and categorical variables were shown as number and percentage values. To determine the mean of the differences between two paired samples, Paired t-test, and Wilcoxon signed-rank test was used. Categorical variables were compared with Mc Nemar test. The association between ERP and EKG parameters was evaluated by Pearson's correlation analysis. A p-value of <0.05 was accepted as statistically significant.

RESULTS

A total of 50 patients with symptomatic WPW syndrome who underwent catheter ablation were enrolled in our study. The clinical and baseline characteristics of the study population are shown in **Table 1**. The mean age of the study population was 35.7±15.1 years, and 52.0% of patients were female, 16.0% of patients had hypertension, 4.0% of patients had diabetes mellitus and 4.0% of patients had coronary artery disease. Four of the patients were smoking and 9 of the patients were using an antiarrhythmic drug.

Table 1. Baseline characteristics of the study patients (n=50)

Age, years	35.7±15.1
Male, n (%)	24 (48%)
Female, n (%)	26 (52%)
Hypertension, n (%)	8 (16%)
Diabetes mellitus, n (%)	2 (4%)
Smoking, n (%)	4 (8%)
Coronary artery disease, n (%)	4 (8%)
Antiarrhythmic drug, n (%)	9 (18%)
LVEF, %	59.2±6.3
ERP of AP, ms	242.8±63.5

Data are given as mean±standard deviation, or n (%). AP: accessory pathway ; ERP: effective refractory period; LVEF: Left ventricular ejection fraction

The electrocardiographic measurements of the study population before and after the procedure are shown in **Table 2**. Heart rate (75.4±11.2 vs 73.8±13.6; p=0.382) was similar but PR (98.5±20.3 vs 153.1±27.4; p < 0.001), QRS (123.3±8.1 vs 94.3±10.9; p<0.001), QT (406.3±33.9 vs 384.8±32.5; p<0.001) and QT(c) (452.6±32.7 vs 422.5±25.5; p<0.001) are significantly different as expected before and after the procedure. Tp-e (86,6±16,2 vs 80.6±12.5; p=0.021) and Tp-e(c) (96.7±18.9 vs 88.3±11.2; p=0.005) intervals showed a significant decrease (**Figure 2**) while JT (283.0±33.1 vs 290.5±30.9; p=0.115) and JT(c) (314.9±31.2 vs 318.6±23.9; p=0.423) intervals were statistically similar after the procedure.

Table 2. Electrocardiographic interval measurements before and after procedure

Parameters	Before procedure	After procedure	p value
Heart rate, bpm	75.440±11.202	73.820±13.621	0.382
PR interval, ms	98.500±20.310	153.100±27.459	<0.001
QRS, ms	123.300±8.057	94.300±10.974	<0.001
QT interval, ms	406.300±33.924	384.800±32.544	<0.001
JT interval, ms	283.000±33.120	290.500±30.876	0.115
Tp-e interval, ms	86.600±16.208	80.600±12.521	0.021
QT(c) interval, ms	452.606±32.708	422.533±25.522	<0.001
JT(c) interval, ms	314.947±31.185	318.634±23.901	0.423
Tp-e(c) interval, ms	96.660±18.900	88.294±11.161	0.005

Data are given as mean±standard deviation, or n (%). Tp-e: T-peak to T-end interval, terminal part of the QT interval, Tp-e(c): corrected T-peak to T-end interval; JT: J point to T-end interval.

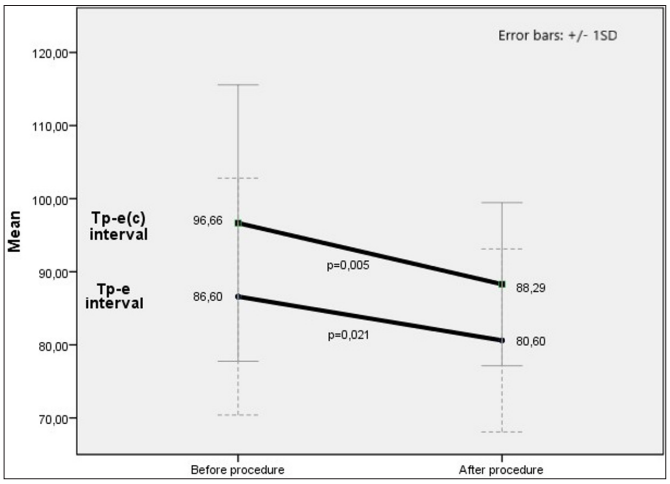

Figure 2. Tp-e and corrected Tp-e intervals showed a significant decrease after catheter ablation.

Calculated electrocardiographic interval ratios of study population before and after the procedure are shown in **Table 3**. While Tp-e/QT (0.213±0.037 vs 0.210±0.030; p=0.549) and Tp-e/QT(c) (0.192±0.035 vs 0.192±0.035; p=0.957) ratios did not show a significant change, Tp-e/JT (0.307±0.053 vs 0.279±0.040; p=0.001) and Tp-e/JT(c) (0.276±0.048 vs 0.255±0.045; p=0.009) ratios showed a significant decrease (**Figure 3**). Tp-e/JT and Tp-e(c)/JT(c) ratios were identical.

Table 3. Calculations of electrocardiographic interval ratio before and after procedure.

Parameters	Before procedure	After procedure	p value
Tp-e/QT ratio	0.213±0.037	0.210±0.030	0.549
Tp-e/QT(c) ratio	0.192±0.035	0.192±0.035	0.957
Tp-e/JT ratio	0.307±0.053	0.279±0.040	0.001
Tp-e/JT(c) ratio	0.276±0.048	0.255±0.045	0.009
Tp-e(c)/JT(c) ratio	0.307±0.053	0.279±0.040	0.001

Data are given as mean±standard deviation or n (%). Tp-e: T-peak to T-end interval, terminal part of the QT interval, Tp-e(c): corrected T-peak to T-end interval; JT: J point to T-end interval

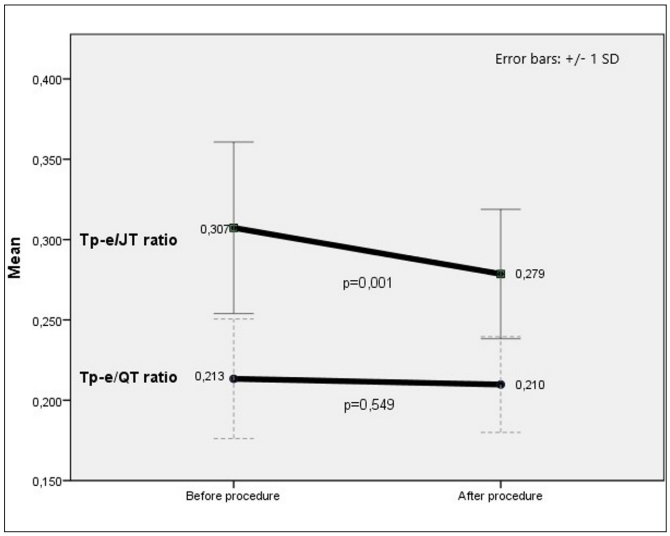

Figure 3. While Tp-e/QT ratio did not show a significant change, Tp-e/JT ratio showed a significant decrease.

Correlation analysis between ERP of the accessory pathway with ECG parameters are shown in **Table 4**. There was a significant association between ERP of the accessory pathway and before procedure Tp-e interval (r=-0.374, p=0.007), Tp-e (c) interval (r=-0.370, p=0.008, **Figure 4a**), Tp-e/JT ratio(r=-0.371, p=0.008, **Figure 4b**).

Table 4. Correlation analysis between ERP of the AP and ECG parameters

Parameters	Correlation coefficient (r)	p-value
Tp-e interval before procedure	-0.374	0.007
Tp-e interval after procedure	-0.214	0.135
Tp-e (c) interval before procedure	-0,370	0.008
Tp-e (c) interval after procedure	-0.105	0.467
Tp-e/JT ratio before procedure	-0.371	0.008
Tp-e/JT ratio after procedure	-0.143	0.320

AP: accessory pathway; ERP: effective refractory period; Tp-e: T-peak to T-end interval, terminal part of the QT interval, Tp-e(c): corrected T-peak to T-end interval; JT: J point to T-end interval.

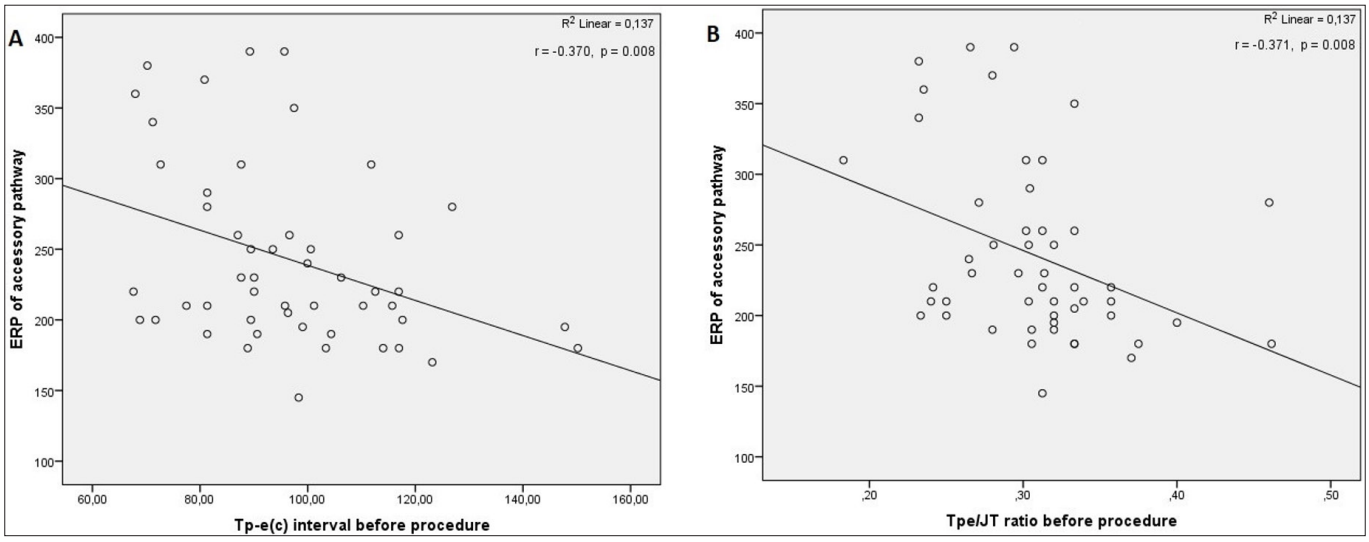

Figure 4. The correlation between effective refractory period (ERP) of the accessory pathway and (A) corrected Tp-e interval, (B) Tp-e/JT ratio before procedure was significant.

DISCUSSION

In the present study, we demonstrated that Tp-e interval and Tp-e/JT ratios were significantly diminished in patients with WPW syndrome after the catheter ablation procedure. This is the first study that demonstrated the relationship between Tp-e interval and Tp-e/JT ratio in patients with WPW syndrome.

In patients with WPW syndrome, it was previously shown that QT and QT(c) were significantly different when the post-ablation ECG was compared to the pre-ablation one, whereas the JT and JT(c) values were unchanged (12). A previous study showed that eccentric ventricular depolarization due to preexcitation did not result in abnormal JT dispersion (12,13). Our study has shown that eccentric ventricular depolarization due to preexcitation does not also result in abnormal JT interval, but it results in longer Tp-e interval which is specified as an index of total dispersion of repolarization (4,14).

Many studies have shown longer Tp-e interval to be associated with higher risk. For example, prolonged Tp-e has been shown to be associated with increased mortality in patients with long QT syndrome (15), and similar findings have been reported in patients undergoing primary percutaneous coronary intervention for myocardial infarction (16). Prolonged Tp-e has been shown to predict VT, sudden cardiac death, or both in patients with systolic dysfunction and implantable cardioverter defibrillators implanted for primary prevention (17). The relationship of longer Tp-e interval with VT also has been described extensively in patients with Brugada syndrome (18). Recently a study showed that Tp-e interval, Tp-e/QT ratio were prolonged in COVID-19 patients with pneumonia (19).

Catheter ablation reduced the frequency of arrhythmic events in a prospective randomized clinical trial of patients with asymptomatic pre-excitation (20). Shortening of Tp-e interval after the ablation in patients with WPW syndrome may be one of the mechanisms explaining this reduction of arrhythmic events after ablation in asymptomatic patients because the longer of Tp-e interval indicates greater dispersion of ventricular repolarization and therefore increased susceptibility to electrical reentry that can cause ventricular tachyarrhythmia (21).

The assumed mechanism of sudden cardiac death and ventricular fibrillation (VF) is rapid stimulation of the ventricular myocardium due to atrial fibrillation rapidly conducted through the accessory pathway (22) however atrial fibrillation is not the only VF initiating arrhythmia as shown by the tachyarrhythmias documented prior to the occurrence of VF (23). We can suppose that pre-excited atrial fibrillation with a fast ventricular response may cause VT due to prolongation of the Tp-e interval in WPW syndrome. The vulnerable period in the cardiac cycle, simultaneous with the downsloping portion of the T wave in the ECG, is a dangerous period for VT. So, a longer vulnerable period means a greater risk for arrhythmia. Similarly, short ERP is one of the risk factors in WPW. This study showed a significant negative relationship between Tp-e or Tp-e (c) and the ERP of the accessory pathway and supported this supposition.

In the early post-ablation period, the qualitative changes of the T wave morphology (T wave memory) are observed. Although it is considered that T wave memory is associated with longer of repolarization in the early activated areas, repolarization changes at the late activated areas were ranging from shortening, minimal, or no change to significant action potential duration prolongation (24,25). In addition, previous reports described these changes in the T wave vector without the changes in the repolarization duration (26,27). Inconsistency in these findings is a subject of an ongoing

discussion. This study showed that Tp-e and Tp-e(c) intervals showed a significant shortening while JT and JT(c) intervals were statistically similar in the early post-ablation period.

Tp-e/QT ratio has been proposed to be a marker of ventricular repolarization (9,28) but, QRS wave abnormalities in WPW patients may preclude accurate measurement of repolarization as assessed by the QT intervals. Therefore, like this ratio, Tp-e/JT can be a marker of ventricular repolarization in WPW syndrome. It is shown that the JT interval such as the QT interval is heart rate (HR) dependent (29). Also, correcting the Tp-e interval using Bazett's formula (Tp-e(c)=Tp-e interval/√ (RR interval) has improved the predictive value of this marker for SCA risk (30). Mathematically, if 'corrected Tp-e/corrected JT' ratio is simplified by the common factor (√ RR interval) of the numerator and denominator, the Tp-e/JT ratio is obtained. Thus, the Tp-e/JT ratio remains constant despite dynamic physiological changes in HR, and it may be a ventricular repolarization index that is independent of HR. Once the use of Tp-e and Tp-e/JT is more investigated, it may become valuable as a part of future multi-component risk prediction algorithms in WPW.

There are some limitations to this study. First, the study has a relatively small sample size. A larger sample size would have strengthened our findings. Then, the relationship between ventricular arrhythmias and both Tp-e interval and Tp-e/JT ratio was not assessed in patients with WPW syndrome. Therefore, long-term follow-up and large-scale prospective studies are needed to investigate the predictive value of the Tp-e interval and Tp-e/JT ratio in patients with WPW syndrome.

CONCLUSION

We demonstrated that the pre-ablation Tp-e interval and Tp-e/JT ratios were significantly diminished in patients with WPW syndrome after the catheter ablation. Long-term follow-up and large-scale prospective studies are needed to investigate the predictive value of the Tp-e interval and Tp-e/JT ratio about mortality and malignant arrhythmias in patients with WPW syndrome.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital, Clinical Researchs Ethics Committee (Date: 2021, Decision No: E1-12-2031).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Goeckerman therapy versus methotrexate for psoriasis: a study on military personnel

Aslan Yürekli[1], Mustafa Tunca[2], Kadir Küçük[3], Ayşenur Botsali[2], Ercan Çalışkan[2]

[1]Kuşadası Public Hospital, Dermatology Clinic, Aydın, Turkey
[2]Gülhane School of Medicine, Department of Dermatology, Ankara, Turkey
[3]Hitit University, Faculty of Medicine, Department of Dermatology Çorum, Turkey

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ABSTRACT

Introduction: Although methotrexate is a widely used systemic medication for psoriasis, a restrictive cumulative dosage limits its use in each patient, and a liver biopsy is recommended when the cumulative dose reaches 3.5–4.0 mg. As an alternative, Goeckerman therapy is a safe, efficient, tar-based method of treating psoriasis but one used increasingly less in recent decades due to the inconvenience of tar application and of requiring outpatients to remain covered in tar before receiving phototherapy hours if not a day later. However, for patients such as soldiers who can be treated as inpatients, Goeckerman therapy is preferable due to its efficacy and good safety profile.

Material and Method: We retrospectively evaluated 96 patients with psoriasis, all military personnel, who had been treated with either methotrexate (n=49) or Goeckerman therapy (n=47) between 2012 and 2016. Their baseline and exit Psoriasis Area and Severity Index (PASI) scores were comparatively analyzed.

Results: No statistical difference in relative recovery emerged between patients who had received methotrexate and ones who had undergone Goeckerman therapy. Both groups had achieved a mean PASI score of 75 at approximately the same time.

Conclusion: When the rapid return to work is important, we recommend using Goeckerman therapy to treat psoriasis given its relatively low side effect profile and lack of immunosuppressive action. Both advantages can benefit patients such as soldiers who are able to undergo treatment in inpatient settings, cannot meet physicians frequently due to work requirements, and cannot avoid the risk of infection (i.e., a risk factor for methotrexate use) due to living in crowded spaces.

Keywords: Goeckerman therapy, methotrexate, psoriasis vulgaris, coal tar, phototherapy

INTRODUCTION

Psoriasis is a chronic, multifactorial, inflammatory disease that affects an estimated 2–3% of the world's population. Although psoriasis can emerge at any age, the age of onset shows a bimodal peak at 20–30 and 50–60 years, and environmental, genetic, and immunological factors appear to play a role in its development (1). As for its pathophysiology, the activation and migration of T cells to the dermis triggers the release of cytokines, which causes inflammation and the rapid production of keratinocytes (2). Various treatment options are available for psoriasis, including topical agents, systemic agents, and phototherapy (3).

The analog of folic acid, methotrexate is used as an antineoplastic agent and to treat inflammatory disorders such as psoriasis as well as dermatomyositis, lupus erythematosus, sarcoidosis, and systemic sclerosis (4). As an inhibitor of dihydrofolate reductase, methotrexate also inhibits the synthesis of folate (5,6). Methotrexate was approved for the treatment of severe, recalcitrant, disabling psoriasis by the U.S. Food and Drug Administration in 1972. Although its maximum effects are generally achieved within 5 to 6 months, methotrexate usually shows some benefit within 6 to 8 weeks in response to skin diseases (4).

Goeckerman therapy can also be used to treat moderate to severe plaque psoriasis. First formulated in 1925 by William H. Goeckerman, the therapy involves the combined application of crude coal tar and broadband ultraviolet-B (UVB), although narrow-band UVB may be used instead (7). Although the tar has to remain on the skin for at least 2 hours, clinic practice recommends extending the application overnight and thus applying the

Corresponding Author: Aslan Yürekli, aslanyurekli03@hotmail.com
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tar at bedtime, which also precludes the inconvenience of the smell and staining during the day (8).

Because the patient has to wait covered in tar for some time and because the application of tar stinks, stains clothes, causes mechanical discomfort, and thus reduces treatment compliance, Goeckerman therapy is not preferred in practice. However, in terms of efficacy and reliability, the therapy is indispensable for clinicians and may thus be preferable over other treatments for patients who can be treated in inpatient settings.

MATERIAL AND METHOD

The study was carried out with the permission of Gülhane School of Medicine Non-Interventional Clinical Researchs Ethics Committee (Date: 08.03.2016, Decision No: 3-117). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. After a local ethics committee approved our study, we evaluated the data of patients with psoriasis who were treated at our clinic with methotrexate or Goeckerman therapy between 2012 and 2016. Clinical outcomes were obtained by screening outpatient and clinical records. Once patients without complete data in their medical records were screened out, 96 patients remained and were included in our sample. Whereas 49 of them had received methotrexate treatment, the 47 others had undergone Goeckerman therapy. All of the patients were military personnel, and none had received any adjuvant therapy.

In the group of patients who had received Goeckerman therapy (i.e., Goeckerman group), a mixture containing 5% coal tar and 2% salicylic acid had been applied to the entire body, left for 10 hours overnight, and removed in the morning with liquid petroleum jelly. Once the patients had bathed, they proceeded to the phototherapy unit to receive broadband UVB phototherapy. The initial dose to be administered to each patient had been determined according to their Fitzpatrick skin type. The patients underwent the entire procedure described above for five days, during which erythema responses were assessed on a daily basis and doses adjusted accordingly.

In the group of patients who had been treated with methotrexate (i.e., methotrexate group), 10–25 mg of methotrexate per week had been subcutaneously administered to each patient for six weeks. To reduce the frequency of side effects, each patient had also received 5 mg of folic acid every day except on the day of methotrexate administration.

We retrospectively assessed the efficacy of the treatments in light of baseline and exit Psoriasis Area and Severity Index (PASI) scores, and each patient's time to reach a PASI score of 75 was determined.

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The Mann–Whitney U test was used to analyze the age, baseline PASI score, and time to reach a PASI score of 75 in each group.

RESULTS

All patients were male. In the Goeckerman group, the mean age of patients was 26.1±6.7 years, and the baseline PASI score (M ±SD) was 14.1±2.6 (**Table 1**). By little contrast, the mean age in the methotrexate group was 26.7±5.2 years, and the baseline PASI score was 14.3±2.3. Thus, as shown in Table 2, no statistically significant difference emerged between the treatment groups in terms of age (p > .355) or baseline PASI score (p>.464). Likewise, the time to achieve a PASI score of 75—26.1±5.08 and 25.8±5.95 days in Goeckerman and methotrexate groups, respectively—did not significantly differ between the groups (p>.790) (**Table 2**).

Table 1. Characteristics of patients

Treatment	Age in years	Initial PASI score
Goeckerman therapy	26.1±6.7	14.1±2.6
Methotrexate	26.7±5.2	14.3±2.3
p	>.05	>.05

Table 2. Response to treatment (day)

Treatment	Response to treatment (day)	
Goeckerman therapy	26.1±5.08	p>.05
Methotrexate	25.8±5.95	p>.05

DISCUSSION

Topical agents play an important role in treating psoriasis and can be combined with all treatment options. Such agents modify the permeability of skin lesions to increase the transmission of UV rays and thus improve therapeutic efficacy. Among such agents, topical tar has been used to treat dermatological conditions for years, especially as part of Goeckerman therapy, which is as effective as other treatments in treating psoriasis and relatively safe (9). Both the tar and UVB used in the therapy have been hypothesized to inhibit the hyperproliferation of keratinocytes, modulate inflammatory cytokines, and deplete T lymphocytes when used together, all for an increased cumulative effect (10). Regarding remission, the therapy has also been more successful than other phototherapy regimens.

Goeckerman therapy originally consisted of soaking in crude coal tar day and night, followed by gradually increasing exposure to UV radiation after the tar was removed. Although the tar should stay on the body for at least 2 hours, the longer the application, the better the results (9). Side effects of the topical application of

raw coal tar include tar folliculitis, acneiform sputum, contact dermatitis, acute tar toxicity and atrophy, telangiectasia, pigmentation, exfoliative dermatitis, and, far more rarely, keratoacanthomas (10). In regard to the remission periods, Goeckerman therapy is proven to be more succesful than the other phototherapy regimens.

The most concerning side effect of Goeckerman therapy is the increased risk of skin cancer. Despite the proven carcinogenic effects of PUVA, those effects remain controversial when UVB is used. In a study with 1,373 patients, Stern et al. (11) found that patients who had received recurrent Goeckerman therapy showed an increase in skin cancer. By contrast, Studniberg et al. (12) have reported that available data indicate that therapeutic UVB poses a low risk of producing cutaneous cancers, with the possible exception of producing ones on male genital skin, whereas oral PUVA poses a definite cutaneous carcinogenic risk. In the same vein, Hearn et al. (13,14) observed no significant association between NB-UVB treatment and BCC, SCC, or melanoma, despite a small increase in BCC among patients treated with PUVA.

Methotrexate, formerly known as amethopterin, is a chemotherapeutic agent that affects the immune system by competitively inhibiting dihydrofolate reductase, an enzyme involved in the synthesis of tetrahydrofolate. Methotrexate's efficacy against psoriasis is apparent from its antiproliferative and anti-inflammatory effects (4). The dose may be gradually increased until the clinical response is achieved but should not exceed 30 mg/week, and treatment should be continued with the lowest dose that achieves remission. To reduce the frequency of side effects, oral folic acid supplementation of 1–5 mg should also be given daily except on the day of methotrexate administration (4,5). Before treatment, the patient should receive a physical examination and their medical history should be comprehensively evaluated, especially for the likelihood of alcohol intake, exposure to hepatitis B or C, and familial liver disease. Laboratory tests, including a CBC with differential, creatinine, and liver function tests for albumin and bilirubin, should be obtained for baseline levels, and a purified protein derivative test or another screening test for latent tuberculosis should also be conducted at baseline, particularly if the patient's history indicates risk. When risk factors are absent, a liver biopsy should be performed when the cumulative dose of methotrexate reaches 3.5–4.0 g. If risk factors such as alcoholism, a high level of liver enzymes, and obesity are present, however, then a liver biopsy should be performed when the cumulative dose reaches 1.5–2.0 g (15-17). The most common adverse effects of methotrexate include hepatotoxicity, ulcerative stomatitis, leukopenia and, thus predisposition to infection, nausea, abdominal pain, fatigue, fever, dizziness, acute pneumonitis, and, more rarely, pulmonary fibrosis and kidney failure. Because methotrexate is teratogenic, it is not used in pregnancy (18-20).

In our retrospective study, conducted on a subpopulation of military personnel—that is, individuals who cannot be required to visit physicians frequently due to their work-related responsibilities and who cannot avoid the risk of infection because they live in crowded spaces—patients had been treated with either Goeckerman therapy or systemic treatment for a similar period of time. We examined the use of Goeckerman therapy given its advantages for return to work as a method that does not require follow-up after hospitalization. In treatment with methotrexate, however, patients have to be followed up during the treatment period and in the weeks that follow and cannot be present in crowded workplaces due to the risk of infection.

Because we examined a subpopulation available for treatment requiring hospitalization and for whom it is important to avoid the side effects of methotrexate treatment, whether the effectiveness of Goeckerman therapy is similar to that of systemic therapy in other specific populations should be examined in future studies.

CONCLUSION

Although Goeckerman therapy is a largely forgotten treatment, it remains effective and reliable for treating psoriasis. In our study, we found similar effects between Goeckerman therapy and methotrexate. However, given its lower side effect profile, Goeckerman therapy should be used more widely among patients such as military personnel who can be treated as inpatients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gülhane School of Medicine Non-Interventional Clinical Researchs Ethics Committee (Date: 08.03.2016, Decision No: 3-117).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

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Evaluation of the quality and the content of YouTube videos in Turkish on protection from coronavirus

Mustafa Alparslan Babayiğit
Public Health Specialist, Private Occupational Physician, Ankara, Turkey

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ABSTRACT

Aim: This study aimed to evaluate the videos in Turkish on protection from coronavirus published on YouTube in terms of general quality and content.

Material and Method: Search on YouTube website "coronavirus; protection "in line with the keyword" all the time, Turkey and the Turkish language "was held. Among the first 100 results, 63 non-repetitive and completely ad-free videos with a duration of 1-40 minutes were included in the study. The person or institution who provided the information for each video, the video length, the number of views, the number of likes and dislikes were recorded. The Global Quality Scale (GQS) was used to determine the overall quality of the videos. In addition, a scoring system was created and examined whether the information regarding the 14 rules determined by the Turkish Ministry of Health to protect the public from coronavirus was found or not in the published videos.

Results: While 50.8% (n=32) of the videos analyzed in this study were personal sharing videos for educational and informative purposes, 31.8% (n=20) of them were TV health /news programs. While 71.2% of those who provided information in the videos were medical doctors, 26.9% were out of health. When the general quality of the videos is evaluated according to the GQS scale; It was determined that 39.7% (n=25) of them were of medium quality, and 30.2% (n=19) of them were of good quality.

Conclusion: As a result of our study, it was determined that the videos that contain at least five rules and have practical application content are of better quality. In pandemic periods when preventive measures are superior to treatment, effective use of social media platforms should be ensured to raise society's awareness.

Keywords: Coronavirus, prevention, YouTube

INTRODUCTION

COVID-19, caused by the SARS-COV-2 virus, was declared a pandemic in March 2019, starting from the Wuhan province of China and spreading worldwide. Because COVID-19 is a new clinical entity, clinical information was limited in the early stages of the pandemic. However, as the process progressed, information about the disease increased (1).

As the transmission routes, clinical course, and prevention methods of the SARS-COV-2 virus were determined, the relevant experts informed the society through newspapers and television. Thus, the epidemic was tried to be brought under control. Apart from this, information is shared via the internet. Especially the free and easily accessible video-sharing site YouTube has become a preferred platform as a source of information about COVID-19 (2).

Raising public awareness about transmission routes and prevention methods is vital in essential public health (3). However, sharing on the internet is made by different people and institutions apart from the relevant experts. Therefore, apart from correct information, false and misleading messages can be given.

In order to control the epidemic and protect public health, it is necessary to monitor the content of the messages given to the society. In this study, it is aimed to evaluate YouTube videos, which are used as a source of information in protection from COVID-19, in terms of content and quality (4).

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Corresponding Author: Mustafa Alparslan Babayiğit, musalpbaba@yahoo.com **Received:** 10.11.2021 **Accepted:** 17.12.2021

to evaluate YouTube videos, which are used as a source of information in protection from COVID-19, in terms of content and quality.

MATERIAL AND METHOD

This study was conducted as a YouTube research, there is no need for ethics committee approval.

"Coronavirus; In line with the keywords "protection", a search was made on 10.07.2021 for "all times, in Turkey and Turkish language". Among the top 100 results, videos with a duration of 1-40 minutes, non-repetitive and completely ad-free were included in the study for review. The researcher evaluated a total of 63 videos, which were found to meet the criteria for inclusion in the research. For each video, the person or institution providing the information, the length of the video, the number of views, the number of likes and dislikes were recorded.

The Global Quality Scale (GQS) was used to determine the overall quality of the videos. The GQS is a five-point Likert scale based on the quality of information, the flow of information found online, and ease of use, with 1 point very bad, 2 points bad, 3 points fair, 4 points good and 5 points excellent quality. Besides, it was examined whether the information about the fourteen rules determined within the scope of the video titled "14 Rules that will protect you and Turkey from the risk of coronavirus", prepared by the Republic of Turkey Ministry of Health to protect the public from coronavirus, is available in the published videos (5). A "MH scoring system" was created by giving 1 point if each question is in the video and 0 points if not. Accordingly, the videos were scored 0-14 points.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyzes were performed with the Kolmogorov-Smirnov Goodness of Fit Test. In addition, the T-Test was used to analyze two groups when the data conformed to the normal distribution, and the Mann-Whitney U-Test was used when they did not. Analyzes were performed with IBM SPSS (Statistics Package Program for Social Sciences) version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was considered as $p<0.05$.

RESULTS

While 50.8% (n=32) of the YouTube videos on protection from coronavirus were personal sharing videos for educational and informational purposes, 15.9% (n=10) were TV health programs, 15.9% (n=10) TV news program and 17.5% (n=11) were hospital videos. While 71.2% of the informants in the videos were medical doctors, 26.9% were non-health people. Video length median 4.0 (1-38.4) min. While the number of views was 2739 (25-650,994), the median value on the day of publication was 234 (31-277), the number of likes was 40 (0-14000), the number of dislikes was 1 (0-570).

In 54.0% of the videos, the definition and/or complaints of the coronavirus-related flu infection were stated, 57.1% of the videos were about the route of transmission, 31.7% of the risk group was mentioned, 52.4% of them were alcohol-based in cases where handwashing is not possible. It was determined that the use of hand disinfectant or cologne was recommended. Washing hands, wearing masks, etc., in only 12 videos (19%). It was determined that the practical applications of the precautions were included.

When the general quality status of the videos was evaluated according to the GQS scale; It was found that 39.7% (n=25) was of medium quality, 30.2% (n=19) was of good quality, contained important information sufficiently, only some information was not included, and was beneficial for patients, whereas 20% It was determined that 0.6 of them (n=13) were generally of poor quality and some of the information for patients was accurate and provided very limited benefit.

In the videos examined within the scope of the research, the most frequent hand washing (85.7%), keeping a distance (60.3%), avoiding close contacts (55.6%), not touching the eyes, mouth, and nose with the hands (49.2%) and the common cold. In addition, it was determined that the subjects wearing a mask in case of symptoms (49.2%) were mentioned. Not sharing personal belongings (7.9%), canceling or postponing international travels (9.5%), washing clothes at 60 to 90 degrees (9.5%), and frequently ventilating indoor environments (19%) level (**Table 1**).

When the videos that contain at least 5 of the 14 rules determined by the Ministry of Health to protect the public from coronavirus, and the videos that express more rules in their explanations; The median values of the General quality (GQS) scale [4 (2-5)] were found to be statistically significantly higher in videos with an MH. score of >5 than those with an MH. score of ≤ 5 [2.50 (1-3)] ($p<0.05$).). It was also found that videos with an MH score of >5 included a higher rate of practical applications (29.0% vs. 9.4%) ($p<0.05$) (**Table 2**).

Table 1. Availability of information on 14 rules prepared by the Ministry of Health, which will protect them from the risk of coronavirus, in the published videos

	14 Rules that will protect you from the risk of the Coronavirus	Yes (n,%)	No (n,%)
1	Wash your hands frequently with soap and water for at least 20 seconds by scrubbing.	54 (85.7)	9 (14.3)
2	Cover the mouth and nose with disposable wipes when coughing or sneezing, use the inside of the elbow if there is no wipe.	30 (47.6)	33 (52.4)
3	Do not touch your eyes, mouth and nose with your hands.	31 (49.2)	32 (50.8)
4	Have distance of at least 3-4 steps from people who show symptoms of a cold.	38 (60.3)	25 (39.7)
5	Cancel or postpone your travels abroad.	6 (9.5)	57 (90.5)
6	Spend the first 14 days at home on your return from abroad. Do not accept visitors during the time spent at home and isolate yourself.	12 (19.0)	51 (81.0)
7	Ventilate your room frequently.	12 (19.0)	51 (81.0)
8	Clean frequently used surfaces such as door handles, fixtures and sinks with water and detergent every day.	17 (27.0)	46 (73.0)
9	Do not share your personal belongings such as towels.	5 (7.9)	58 (92.1)
10	Wash your clothes at 60-90°C with regular detergent.	6 (9.5)	57 (90.5)
11	Avoid physical contacts such as handshaking and hugging.	35 (55.6)	28 (44.4)
12	For a strong immune system, drink plenty of fluids, eat a balanced diet, pay attention to your sleep patterns.	28 (44.4)	35 (55.6)
13	If you have cold symptoms, stay away from the elderly and from patients with chronic diseases and do not go out without wearing a mask.	31 (49.2)	32 (50.8)
14	If you have persistent fever, cough and shortness of breath, go to a health facility wearing a mask.	15 (23.8)	48 (76.2)

Table 2. Comparison of videos on protection from coronavirus published on YouTube according to the MH scoring system

	MH score ≤ 5 (n=32)	MH score>5 (n=31)	p
Video length [median(min-max)]	4.09 (1-38.4)	3.44 (1-25.4)	0.290*
How many days has it been on the air?[median (min-max)]	234.5 (31-273)	234 (194-277)	0.659*
Number of views [median (min-max)]	2262 (25-650.994)	5839 (48-648.451)	0.680*
Number of likes [median (min-max)]	31 (0-9200)	76(1-14000)	0.346*
Number of unlikes [median (min-max)]	2 (0-570)	1(0-320)	0.529*
General quality (GQS) scale mean score (Mean±Sd)	2.50 (1-3)	4 (2-5)	<0.001*
Category (n,%)			0.187**
TV health program	8 (25.0)	2 (6.5)	
TV News program	5 (15.6)	5 (16.1)	
Personal sharing	13 (40.6)	19 (61.3)	
Hospital	6 (18.8)	6 (18.8)	
Person giving information (n,%)			0.923**
Doctor	18 (56.3)	2 (6.5)	
Other health personnel	3 (9.4)	5 (16.1)	
Out of health	8 (25.0)	19 (61.3)	
Newsreader	3 (9.4)	3 (9.7)	
Practical application (n,%)			0.047**
No	29 (90.6)	22 (71.0)	
Yes	3 (9.4)	9 (29.0)	

* Mann Whitney U Test, ** Chi-square Test

DISCUSSION

YouTube is a platform where millions of videos are watched every day in over 100 countries. It is used not only for entertainment purposes but also for sharing and receiving information in education, culture, and science (6). The number of shares related to health is also substantial.

In studies in the United States and Poland, it has been observed that there has been a significant increase in accessing health-related information over the internet in the last year; this rate increases even more as the level of education increases, reaching up to 98% among university graduates (7-9). Therefore, the main risk in sharing medical issues on the YouTube video-sharing site is that the person sharing can upload videos regardless of their education, medical equipment, professionalism, and purpose. For this reason, there are concerns about the accuracy, reliability, and usefulness of the shared information for society.

Videos shared on YouTube on many medical topics such as myocardial infarction, cancer, intubation, vaccination, and epidemics have been examined in terms of content

and quality (10-16). While these studies show that video sharing on medical topics has increased in recent years, they also reflect concerns about reliability. Significantly during the pandemic process, the importance of sharing health information has increased. Since COVID-19 pneumonia is new in the literature, it has caused society and the health community concerns. Since the initial study results took time, case reports, individual experiences, and recommendations spread rapidly in magazines, newspapers, and video sharing sites. As a result of our study, it was seen that half of the Turkish internet videos providing information about COVID-19 on YouTube were individual personal sharing, the majority of them were made by doctors and were useful. Similar results have been found in previous studies on YouTube video sharing in H1N1 influenza and Ebolavirus outbreaks (10,11).

In the study of D'Souza et al. (2), 113 videos containing information about COVID-19 were examined and it was seen that 69.9% of them contained useful information, and news programs had a high share of useful information.

In addition to correct, conscious informative sharing, false and misleading information about COVID-19, which is spread unconsciously or intentionally, is spreading rapidly and widely on the internet, threatening public health. In a study examining a total of 240 COVID-19 related videos in six different languages, 52.5% of the videos were found to be informative. However, it has been determined that ten percent of the videos contain medically misleading information, and independent individuals who make individual posts are responsible for 75% of the misleading content (17). Researchers have stated that health authorities such as the CDC, WHO should be included on video sharing sites.

Li et al. (4) reported that 69 COVID-19 related videos that met the criteria were included in their study, and 27.5% of them contained untrue information. They concluded that to contain the COVID-19 outbreak, public health agencies should use YouTube more effectively to provide timely and accurate information and minimize the spread of misinformation.

In the study of Ataç et al. (18), 101 Turkish and 67 English videos were examined and compared. It was found that the total content index was higher in Turkish videos. It has been observed that 23 of these videos are misleading, 65.2% of them are broadcast on news channels, and the average number of views, viewing rates, and video power scores of misleading videos are higher than valuable videos. It is worrying that misleading videos are being presented on news channels, which are watched more.

In order to prevent the spread of the epidemic, society should be informed about the identification, treatment, and isolation of the diseased people, as well as the precautions to prevent the transmission of the SARS-COV-2 virus, hygiene rules, and what to do in suspicious clinical situations. Given its popularity and easy accessibility, YouTube appears to be a virtual platform suitable for this purpose.

In the videos we examined, it was seen that basic hygiene rules and essential protective practices such as hand washing, maintaining social distance, avoiding close contacts, not touching the eyes, mouth, and nose, and wearing a mask in case of cold symptoms were mentioned. Furthermore, It was determined that the GQS scale mean scores of the videos that scored above 5 points in the MH scoring system, which we created according to the fourteen rules prepared and published by the Ministry of Health, were also significantly higher (5). In addition, it was found that practical applications in these videos were statistically significantly higher. Therefore, we believe that these videos have an essential contribution to raising public awareness.

The number of videos, changes in their content over time, and the evaluation of videos belonging to a single site as a video sharing site can be seen as limitations of our study. However, since it is an easily accessible and frequently used video-sharing site, we think it is appropriate for research and evaluation.

CONCLUSION

Video sharing sites such as YouTube attract more attention due to their visuality and are frequently used by internet users. While sharing information from these platforms can be beneficial, it also includes risks in terms of accuracy and reliability. The presence of more traditional medical institutions on these platforms and the supervision of the published videos by a scientific committee in terms of content and quality can play an essential role in being successful and effective in the fight against epidemic diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted as a YouTube research, there is no need for ethics committee approval.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Comparison of the tube thoracostomy techniques on treatment in COVID-19 patients with pneumothorax

Rezan Karaali[1], Hasan Ersöz[2], Pınar Yeşim Akyol[1], Güner Yurtsever[1], Fatih Esad Topal[1]

[1]İzmir Katip Celebi University, Atatürk Training and Research Hospital, Department of Emergency Medicine, İzmir, Turkey
[2]İzmir Katip Celebi University, Atatürk Training and Research Hospital, Department of Thoracic Surgery, İzmir, Turkey

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ABSTRACT

Aim: Tube thoracostomy is an interventional procedure in which there is a high risk for the spread of COVID-19. In this study, we compare the tube thoracostomy procedures performed early on in the pandemic and those performed later after steps were taken in accordance with the new recommendations.

Material and Method: It is a retrospective and single-center study. COVID-19 patients with spontaneous pneumothorax with indications for tube thoracostomy presented to our emergency department between March 10, 2020, and March 31, 2021. Based on the applied tube techniques, two groups were defined; group 1, patients who underwent classical tube thoracostomy, group 2, patients who underwent tube thoracostomy with the recommended preventive measures for COVID-19. The collected data were compared between the two groups.

Results: 106 patients met the study criteria and were included in the study. The difference in the length of the tube duration time between the old or new technique was statistically significant ($p < 0.05$), no difference was identified in the duration of stay, intensive care unit admission, or mortality compared with the two techniques.

Conclusions: In this study, the new measures recommended for tube thoracostomy were found to be effective for the treatment of patients.

Keywords: COVID-19, emergency, pneumothorax, tube thoracostomy

INTRODUCTION

Pneumothorax (PNX) refers to the presence of air between the leaves of the pleura, and can occur as spontaneous, traumatic or iatrogenic. In the case of air >15% in the hemithorax, the treatment is tube thoracostomy (TT) and underwater seal drainage (UWSD) (1). Conventional UWSD bottles have an outlet that can be connected to negative pressure systems, but if it is not connected to the underwater seal drainage system, the air draining from the pleural cavity into the bottle escapes into the room air via this outlet (2-4).

Coronavirus disease-19 (COVID-19), which is still affecting the entire world, involves mainly the respiratory tract and lungs, and is transmitted via droplets. Case reports and studies published since the declaration of the pandemic have shown that PNX may be a symptom of COVID-19 pneumonia, or may occur during the course and treatment of COVID-19 (5-7). As specified in the American Association for Thoracic Surgery (AATS) and British Thoracic Society (BTS) guidelines, all patients requiring hospitalization should be tested for the presence of COVID-19 (3,8). It has been recommended that level 3 personnel protective equipment (PPE) be used for patients requiring interventional procedures, and that COVID-19 be ruled out by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) tests, computed tomography (CT) scans and blood tests. For patients with indications of TT, it is recommended that household bleach (5.25–6.15% sodium hypochlorite) be put into the UWSD bottle at a ratio of 1:50, and a filter be installed on the outlet, as a means of preventing the entry of any viral particles in the air drained from the pleural cavity from mixing with the room air (2-4). As the outbreak has progressed, changes have been made to our approach to PNX patients following the development of treatment guidelines, and the introduction of preventive measures and recommendations.

Corresponding Author: Rezan Karaali, rezantahtaci@hotmail.com
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In this study we compare the TT procedures performed early on in the pandemic and those performed later after steps were taken in accordance with the new recommendations. Our aim in this study is to compare efficiency between these two types of practices on the patient prognosis and mortality.

MATERIAL AND METHOD

Ethical Approval

The study was initiated upon the granting of approval by the Turkish Ministry of Health, dated January 02, 2021 and numbered T21-31-12, and by the İzmir Katip Çelebi University Ethics Committee dated January 21, 2021 and numbered 003. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All persons included in the study signed the an Informed Consent Form.

Study Population

Included in this, retrospective and single-center study were patients with spontaneous PNX with indications for TT who presented to our emergency department between March 10, 2020 and March 31, 2021.

Since the onset of the pandemic, the initial assessment and intervention of PNX patients with indications of TT who present to the emergency department of our hospital have been carried out with the assumed presence of COVID-19. Patients who are to receive TT are taken to a confined intervention area and the intervention is performed by an emergency medicine specialist, an emergency medicine assistant and a member of the allied healthcare personnel, all of whom wear level 3 PPE. As of June 2020, in line with the published recommendations, sodium hypochlorite has been placed in the UWSD bottles and a High-Efficiency Particulate Arrestance (HEPA, Meditera-Altech®) filter has been fixed to the outlet (**Figure 1**), in addition to the PPE measures for patients with indications for TT (3,8,9).

Since the COVID-19 outbreak, every patient with indications for hospitalization has been evaluated for COVID-19, with an RT-PCR test (Bio-speedy® COVID-19 RT-qPCR test) performed for every patient, as recommended by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (10). The patients are then transferred to the isolation ward or the intensive care unit, depending on the COVID-19 test result. For patients with negative test results, a control PCR test is performed at their place of residence (10). Included in the study were patients over the age of 18 years who were not pregnant, nontraumatic, who recorded at least one positive test result and who had sufficient data in their records.

Figure 1. Household bleach (1:50) has been placed in the UWSD bottles and a High-Efficiency Particulate Arrestance (HEPA, Meditera-Altech®) filter has been fixed to the outlet

Two groups were defined in the study, based on the applied tube thoracostomy technique:

- Group 1 includes patients who presented prior to June 1, 2020 and who received TT due to spontaneous PNX. In this group, a filter was not installed on the outlet of the UWSD bottle and no sodium hypochlorite was put into the bottle in this group.
- Group 2 includes patients who presented in or after June 1, 2020 and who received TT due to spontaneous PNX. Unlike in Group 1, in this group, a HEPA filter was installed on the outlet of the UWSD bottle, and sodium hypochlorite was placed into the bottle during TT treatments in this group of patients.

Tube thoracostomy of the patients were removed when all three criteria were met in both groups. Those three criteria were complete cessation of the air leak in the pleura, full expansion of the lungs on the chest x-ray of the patients, daily amount of pleural fluid drained equal to or less than 100 ml (8). Tube thoracostomies were removed when all three criteria were matched at the same time on a day.

Study Protocol

The age and gender of the patients were recorded, along with smoking status, and comorbidities were classified as pulmonary and non-pulmonary, along with hospitalization status (intensive care unit/ward), length of stay, tube duration time, body mass index (BMI) and laboratory parameters. Concerning the COVID-19 findings, thoracic CT scans were interpreted based on the Radiological Society of North America (RSNA) criteria (11). The patients were divided into two groups, as denoted above, and the collected data between the two groups were compared. We recorded 30-day mortality in patients, compared between the two groups, and examined the factors affecting mortality.

Statistical Method

The study data were assessed using IBM SPSS Statistics Version 20. The use of parametric or nonparametric tests was decided by analyzing the normality of the quantitative data using the One-Sample Kolmogorov-Smirnov test. Frequency and percentage distribution were calculated for descriptive statistics and mean, standard deviation, median, minimum and maximum values for continuous variables. The Pearson's Chi-Square and Fisher's Exact tests were used to compare categorical variables between groups. Categorical data were expressed as n (number) and percentages (%). The significance of the values was examined by using the Independent T test and the Mann Whitney U tests in the comparison of independent groups.The effect of laboratory values in determining the mortality of the patients was examined by Receiver Operating Characteristic (ROC) analysis and the cut-off values of the variables with statistical differences were calculated. Binary logistic regression model was used to analysis factors affecting mortality.

Statistical significance level was set at $p < 0.05$.

RESULTS

During the study period, 191 patients presented to our emergency department and were diagnosed with spontaneous PNX, among which, 106 met the study criteria and were included in the study. In our patient series, 81.10% were male, and the mean age was 44.46±21.57 and 57.40±21.73/years for the male and female patients, respectively. The demographic characteristics of the patients and distribution of variables are presented in **Table 1**.

TT was performed using the traditional method in 36.80% of the patients. A comparison of the tube duration time of the patients group 1 and group 2 revealed a mean duration of 4.7 days in the 39 patients group 1, and 2.6 days in the 67 patients group 2. The difference in the tube duration time between the group 1 and group 2 patients was statistically significant ($p < 0.05$), although no difference was identified in the duration of stay, ICU/ward admission or mortality associated with the two groups (**Table 1**).

An evaluation of the mortality data revealed that 55.56% of the patients who died were male, the mean age was 66.11±21.00/years, 94.40% were staying in the intensive care unit, the mean length of hospital stay was 17.88±20.45/days and 72.2% had comorbidities. A statistically significant difference was noted in all the above parameters between the non-surviving and surviving patients (**Table 2**).

Another parameter that affected mortality was the laboratory values of the patients (**Table 3**), among which, C-Reactive protein (CRP), International Normalized Ratio (INR) and D-dimer were associated with mortality. CRP had a sensitivity of 55.6% and a specificity of 27.3% for a cut-off value of 38.12 (AUC: 0.694; 95% CI 0.558–0830); INR had a sensitivity of 61.1% and a specificity of 23.9% for a cut-off value of 1.15 (AUC: 0.729; 95% CI 0.579–0.879); and D-Dimer had a sensitivity of 72.2% and a specificity of 29.5% for a cut-off value of 827.5 (AUC: 0.723; 95% CI 0.599–0.848).

In order to determine the variables that may affect the mortality of the patients, the data obtained in the study were analysed with the "Binary Logistic Regression Model". Mortality was determined as the response variable. According to the analysis results, variables with a (p) value below 0.25 ($p<0.25$) are included in the model. However, there is no fundamental variable that can be included in the model and is at a level that will directly affect mortality as a result of the analysis (**Table 4**).

Table 1. Distribution of variables and comparison of tube procedures

Variables	Total patients	Tradiditional TT procedure	Preventive TT procedure	p
	Mean ±SD	Mean±SD	Mean±SD	
Age/year				0.386
Male	44.65±20.69	42.00±17.20	45.72+22.17	
Female	57.40±21.60	51.8 ± 15.70	63.00±26.91	
Tube duration time (days)	3.40 ± 2.16	4.76 ±2.39	2.67 ±1.53	0
BMI (kg/m2)	23.43±3.35	23.64±2.89	23.29±3.62	0.609
Hospitalization duration (days)	10.12±11.35	11.89±13.13	9.08 ±10.12	0.221
Variables	**n (%)**	**n (%)**	**n (%)**	**p**
Number of patients	106 (100)	39 (37)	67 (63)	
Gender				
Male	86 (81.13)	29 (74.36)	57 (85.07)	0.174
Female	20 (18.87)	10 (25.64)	10 (14.93)	
Smoking				0.048
Yes	63 (59.43)	28 (71.79)	35 (52.24)	
No	43 (40.57)	11 (28.21)	32 (47.76)	
None	69 (65.09)	26 (66.67)	43 (64.18)	0.643
Comorbidity				
Pulmonary disease	19 (17.92)	8 (20.51)	11 (16.42)	
Nonpulmonary disease	18 (16.98)	5 (12.82)	13 (19.4)	
Hospitalization Area				
ICU	27 (25.47)	10 (25.64)	17 (25.37)	0.976
Ward	79 (74.53)	29 (74.36)	50 (74.63)	
CT findings				
1st group	51 (48.11)	19 (48.72)	32 (47.76)	0.924
2nd group	55 (51.89)	20 (51.28)	35 (52.24)	
Mortality				
Nonsurvivor	18 (16.98)	8 (20.51)	10 (14.93)	0.46
Survivor	88 (83.02)	31 (79.49)	57 (85.07)	

TT: Tube Thoracostomy ICU: Intensivecareunit, BMI: body massindex, CT: computedtomography, Group 1: RadiologicalSociety of North AmericaType 1-2, Group 2: RadiologicalSociety of North AmericaType 3-4

Table 2. Evaluation of variables in terms of mortality of patients

Variables	Nonsurvivors n (%)	Survivors n (%)	p
Gender			0.006
Male	10 (55.56)	76 (86.36)	
Female	8 (44.44)	12 (13.64	
Smoking			0.225
Yes	13 (72.2)	50 (59.4)	
No	5 (27.8)	38 (40.6)	
Comorbidity			0.001
None	5 (27.8)	64 (72.7)	
Pulmonary disease	6 (33.3)	13 (14.8)	
Nonpulmonary disease	7 (38.9)	11 (12.5)	
CT Findings			0.226
1st group	11 (61.11)	40 (45.45)	
2nd group	7 (38.89)	48 (54.55)	
TT procedure			0.46
Traditional procedure	8 (44.44)	31 (35.26-3)	
Preventive procedure	10 (55.56)	57 (64.77)	
Variables	**Mean±SD (Min-Max)**	**Mean±SD (Min-Max)**	**p**
Age (Year)			0.057
Male	60.20±24.17 (18-96)	43.39±19.59 (18-96)	
Female	73.50±14.42 (42-89)	46.67±20.12 (23-89)	
Total	66.11±21.00 (18-96)	42.98±19.60 (18-96)	
Tube duration time days	4.5±2.21 (1-14)	3.18±2.16 (1-14)	0.18
Hospitalization duration days	17.88±20.45 (2-68)	8.56±7.69 (2-68)	0.01
BMI kg /m2	23.61±3.88 (15.4-31.10)	23.39±13.26 (15.4-32.70)	0.802

TT: Tube Thoracostomy, BMI: body massindex, CT: computedtomography, Group 1: Radiological Society of North America Type 1-2, Group 2: Radiological Society of North America Type 3-4

DISCUSSION

Pandemics require a long-term fight, and healthcare workers are on the front line of this fight, being the occupational group at the highest risk of infection. Special precautions should be taken in applications such as tube thoracostomy that result in air leak in air-borne infections. Therefore, some precautions have been recommended for the tube thoracostomy applications in patients who simultaneously have SARS-CoV-2 infection and PNX. Ceylan et al. (9) and Gedik et al. (12) used a two-bottle technique. In this technique, trap (collection) and underwater seal bottles were used. A high-efficiency particulate air (HEPA) viral filter was placed on the tip of the underwater seal bottle filled only with 200 cc (80%) alcohol instead of water alone. Pieracci et al. (3), and Irons et al. (13), suggested connection of the exit line to the suction in addition to using a HEPA filter. A transmission prevention protocol was used in this present study as was recommended by

Table 3. Laboratorynvalues of patients and evaluation of in terms of mortality

Laboratory parameteres	Total patients	Nonsurvivors	Survivors	p
	Mean±SD Min-max	Mean±SD Min-max	Mean±SD Min-max	
WBC/10⁹/L	13.63± 5.88 4.11-32.95	14.39±5.78 4.41-26.08	13.48±5.93 4.11-32.95	0.414
HCT/%	38.65±5.22 15.92-48	34.15±7.37 15.92-45.4	39.57±4.16 27.9-48	0.001
PLT/ µlt	280.15±124.06 90-883	275.44 ±191.51 90-883	281.11±106.79 114-564	0.224
CRP mg/L	52.21±81.06 0-416.21	106.75±121.39 0.2-416.21	41.05 ±65.65 0-258.42	0.01
INR	1.21±0.58 0.92-6.62	1.65±1.31 0.98-6.62	1.12±0.16 0.92-1.9	0.002
D-DIMER mg/L	941.89 ±1000.16 112-4526	1513.39±1104.95 230-3300	825±941.98 112-4526	0.003

WBC: White bloodcells, HCT: Hematocrit, PLT: platelet, C-RP: C reactive protein, INR: international normalized ratio.

Table 4. Binary Logistic Regression anlaysis of effect of variables on mortality.

Variables in theEquation	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1a						
gender (1)	-20.342	3647.997	.000	1	.996	.000
Tube Technic (1)	55.706	4501.210	.000	1	.990	1558480290115094300000000.000
ICU, ward (1)	210.869	10331.371	.000	1	.984	3.795E+091
Hospitalization duration	1.530	129.016	.000	1	.991	4.617
Tube duration	-23.583	1374.304	.000	1	.986	.000
BMI	3.073	699.781	.000	1	.996	21.602
WBC	-1.357	219.637	.000	1	.995	.257
HCT	-6.166	469.569	.000	1	.990	.002
PLT	-.100	10.959	.000	1	.993	.905
CRP	-.213	24.202	.000	1	.993	.808
INR	104.632	9309.472	.000	1	.991	2.761E+045
D.Dimer	.006	1.141	.000	1	.996	1.006
CT(1)	-61.000	5065.426	.000	1	.990	.000
Constant	53.130	32811.905	.000	1	.999	1185995125559207200000000.000

ICU: Intensive care unit, BMI: body mass index, WBC: white blood cell, HCT: hematocrit, PLT: platelet, CRP: C reactive protein, INR: International normalized ratio, CT: Computed tomography

Ghoniem et al. (4) which was a HEPA filter on the tip of the UWSB and dilute household bleach (5.25–6.15% sodium hypochlorite) with a ratio of 1:50 to the fluid in the water seal.

Although new measures have been recommended for interventions with patients undergoing TT, there has to date been no study showing the clinical significance of these recommendations in literature. Accordingly, the present study is the first clinical research assessing the tube thoracostomy technique applied with transmission prevent recommendations.

In our patient series, 81.10% were male. Previous studies examining the COVID-19 and PNX relationship also found the number of male patients to be higher than women (9,14,15). Furthermore, previous studies evaluating the factors affecting mortality in COVID-19 patients have established a higher rate of mortality in male patients than in female patients. For instance, Williamson et al. (16) reported the male gender and the presence of cardiovascular disease, diabetes and respiratory disease among the comorbidities to be associated with mortality. Zhou et al. (17) found that 70% of the non-surviving patients were male, and identified hypertension and diabetes mellitus as comorbidities affecting mortality. Harrison et al. (18), in turn, reported that 59% of the patients in their study who died were male, and that mortality was increased by the presence of comorbidities such as kidney failure, diabetes mellitus and heart failure. These studies have shown that presence of comorbid diseases such as hypertension, diabetes, renal failure and heart failure is associated with mortality. We classified the comorbidities of our patients as pulmonary and non-pulmonary, but could not identify any association between the pulmonary/non-pulmonary nature of comorbidities and mortality, although the presence of comorbidities was found to be associated with mortality. Considering the COVID-19 positivity of all the patients in this present series, our findings were consistent with these studies evaluating mortality in COVID-19.

The patients in the present study were younger than those reported on in previous studies investigating the relationship between COVID-19 and PNX (9,14,15). When the evaluation was performed in terms of age, the mortality was found to be increased by increasing age of the patients. Similar to this present study, Willimson et al. (16), and Zhou et al. (17), in their study evaluating the factors affecting the mortality in COVID-19 patients, reported that old-age increased mortality. The mortality is increased in patients with old-age due to the impaired immune system and decelerated healing due to inefficient cytokine response secondary to old-age (19). Therefore, we think that the COVID-19 disease is more deadly in elderly patients.

An examination of the CRP, INR and D-dimer laboratory values examined in the present study were found to be associated with mortality. Previous studies have reported inflammatory markers (CRP) to be associated with COVID-19 severity, and COVID-19 infection has been reported to increase the likelihood of thrombosis development, and to increase D-dimer levels, one of the fibrin degradation products (20). Liao et al. (21) and Wu et al. (22) reported D-dimer, coagulation markers and inflammatory markers to be associated with mortality in COVID-19 patients, although according to these studies, and concurring with our findings, the specificity of laboratory markers in predicting prognosis in COVID-19 patients is limited, needing to be assessed together with the patient's clinical picture.

When the tube techniques were compared; the number of days of tube duration was lower in the patients administered the preventive procedure (group 2) than in those administered the traditional procedure (group2). We suggest that the result we achieved is important since the criteria for discontinuation of the tube were same in both groups. As an explanation for this, while there was limited information on the course of COVID-19 in the early days of the pandemic. We have seen that we can more efficiently treat COVID-19 with increasing knowledge on the disease and new recommendations for treatment have been published. PNX was found to be regressed rapidly due to the effective treatment of the SARS-CoV-2 infection in the lungs in patients who were treated after June 2020. Also, tube duration time was found to be shorter in these patients due to the sufficient expansion of the lungs. In addition, we suggest that healing was more rapid in these patients since the viral load was lowered due to the prevention of viral contamination of the room air by placement of an hypochlorite acid added filter to the exit hole of the USWB. HEPA filters are known to capture particles that are 0.3 μm in size. The size of droplets is 0.5 μm. Although the size of SARS-CoV-2 virus is 0.07–0.09 μm, it will be trained by the HEPA filter as it is transmitted via droplets (23). When draining air from the pleural cavity of patients, the SARS-CoV-2 virus would pass up the thoracostomy tube to the UWSD bottle, and from there into the ambient air.We consider that the spread was prevented by placement of a filter to the exit hole of the UWSD and adding hypochlorite acid into the bottle. The study by Duffy et al. (24) supports this thesis Duffy et al. (24) used an experimental set-up in their analysis of the two modes of administration to measure the particle count in the air in the UWSD bottle through air-leak in the laboratory setting, and recorded a significantly reduced particle emission count when the HEPA filter was installed on the outlet when compared to a set-up without a filter.

When the two tube application techniques were compared, no difference was noted in intensive care unit admissions, the duration of hospital stay and mortality of the patients group 1 and group 2. It can be interpreted from these findings that the transmission preventive recommendations do not have adverse effect on the treatment or prognosis of the patients.

This study has some limitations. The most significant limitation of our study is its retrospective and single-center design and the limited number of patients. Tube thoracostomy procedures were performed in the emergency service and the patients were hospitalized to the appropriate wards and intensive care units. It cannot be determined whether any contamination occurred from these patients to the healthcare service providers since the healthcare providers contacting these patients were also involved in the treatment and follow-up processes of other patients as well.

CONCLUSION

In conclusion, tube thoracostomy is an interventional procedure with a high risk of contamination for droplet transmitted diseases such as COVID-19 that involve the respiratory tract. It has been suggested to put hypochlorite acid in the tube thoracostomy bottle and a filter in the outlet hole in order to prevent infection of the healthcare workers who perform this procedure. This is a cheap, simple and easily available protocol. In this study, we evaluated the effect of this procedure on patients. According to the results we obtained, we found that the new recommendations do not have an adverse effect on the patient. In light of the experience we gained from the SARS-CoV-2 pandemics, we consider that transmission preventing protocols should be continued even after the pandemic is over. Large scale multicenter studies are required in order to develop and standardized new protocols.

ETHICAL DECLARATIONS

Ethics Committee Approval: It was approval by the Turkish Ministry of Health, dated January 02, 2021 and numbered T21-31-12, and by the İzmir Katip Çelebi University Ethics Committee dated January 21, 2021 and numbered 003.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Evaluation of caregiver burden of cancer patients and impact of this burden on caregiver's quality of life

Erkan Erdur[1], Özgen Ahmet Yıldırım[1], Kerem Poyraz[2], Halil Kömek[3], Metin Yaman[4], Mustafa Çelik[5]

Gazi Yaşargil Training and Research Hospital, Department of Internal Medicine, Division of Medical Oncology, Diyarbakır, Turkey
Gazi Yaşargil Training and Research Hospital, Department of Radiation Oncology, Diyarbakır, Turkey
Gazi Yaşargil Training and Research Hospital, Department of Nuclear Medicine, Diyarbakır, Turkey
Gazi Yaşargil Training and Research Hospital, Department of Internal Medicine, Diyarbakır, Turkey
Gazi Yaşargil Training and Research Hospital, Department of Psychiatry, Diyarbakır, Turkey

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ABSTRACT

Aim: To predict the caregiver burden based on the clinical characteristics of cancer patients and the social and economic circumstances of the caregiver, and to evaluate the influence of this burden on the caregiver's quality of life.

Material and Method: The effects of the clinical findings of 411 patients followed up and treated in our clinic between January 2020 and March 2021, and the social and economic circumstances of the caregiver on the Zarit caregiver burden questionnaire score filled by the caregivers were analyzed. In addition, the Zarit caregiver burden score obtained was researched how influenced the Short-form 36 quality of life questionnaire filled by the caregivers.

Results: In our study, a statistically significant correlation was found between Zarit score and ECOG PS, transportation, residence status, receiving chemotherapy, having a metastatic disease ($p<0.05$ for all) in linear regression analysis of Zarit score with pairwise and more than two groups analysis. A moderate reverse relationship was determined between the Zarit scores of caregivers and SF36 scores ($p<0.05$ for all).

Conclusion: The caregiver burden is affected by the patient's clinical characteristics and the social and economic circumstances of the caregiver. Increasing the caregiver burden has adverse effects on the caregiver's quality of life. These findings show the importance of considering the caregiver factor in the evaluation of treatment compliance and well-being of patients.

Keywords: Cancer, caregiver burden, zarit caregiver burden questionnaire, short form 36

INTRODUCTION

Approximately 19.3 million new cancer cases were diagnosed globally in 2020; meanwhile, 10 million cancer patients died due to this disease (1). Cancer, responsible for one out of every six deaths globally, is the second most common cause of death after cardiovascular-related deaths (2). Despite today's contemporary diagnosis and treatment protocols, the potentially fatal cancer disease and its treatment have devastating effects on patients physically and psychologically.

Relatives, spouses, and close friends who have a meaningful personal relationship with the patient, take care of the cancer patient, and provide a wide range of help are also affected by the psychological and physical trauma of the cancer disease (3).

Patients with a diagnosis of cancer often require direct support by a caregiver to assist with activities of daily living, administer medications, provide transportation, prepare meals, manage finances, sustaining medical care, and provide emotional support. Caregiving is hard work. About a quarter of the caregivers of cancer patients spend more than 40 hours in a week providing this support to their family or friends (4).

Increasing day by day, more evidence demonstrates that individuals exposed to caregiver burden experience psychological, behavioral, and physiological effects that may contribute to impaired immune system function, coronary heart disease, and premature death compared to non-caregivers (5-6). Therefore, caregivers of cancer patients remain under both psychological and physical

Corresponding Author: Erkan Erdur, erdurerkan@gmail.com
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stress and have a lower quality of life by comparison with non-caregivers. Furthermore, caregiver burden and quality of life (QoL) have been investigated in various diseases, including dialysis and transplant recipients, chronic kidney disease, schizophrenia, Parkinson's disease, inflammatory bowel disease, and Alzheimer's disease(7-10). So, we aimed to evaluate the caregiver burden, quality of life, and health perception of the caregiver based on the clinical characteristics of the patients and the social and economic conditions of the caregiver in this study. Providing a systematic quality of life analysis and caregiver burden monitoring of the caregiver of cancer patients was intended with the results we obtained. In addition to this, we aimed to form a referrer guide about the rational and practical distribution of social services provided to patients and their caregivers during cancer treatment has an escalating economic burden.

MATERIAL AND METHOD

This study received approval from the Institutional Review Board of Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (Date 09.06.2021; Decision No: 829). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Primary caregivers of 468 patients with a performance score of 3 or less, followed up for at least three months in Diyarbakır Gazi Yaşargil Training and Research Hospital Medical Oncology Polyclinics between January 2020 and March 2021, were included in this descriptive cross-sectional study. The clinical characteristics of the patients were recorded considering the examination in the last outpatient visit, and a medical oncology specialist evaluated the findings. Zarit Caregiver Burden Interview (ZCBI) and Short Form 36 (SF-36) were filled in by the primary caregivers of the patients in the same conditions in the medical oncology meeting room. All caregivers who were the primary caregivers of a patient diagnosed with cancer and were older than 18 years of age and could read and write in Turkish without significant comorbidity or limitation of the movement were included in the study. 57 of 468 primary caregivers were excluded from the study because of uncontrolled diabetes, uncontrolled hypertension, cardiovascular and cerebrovascular disease, language problems, and purchasing care services. 411 patients and their primary caregivers were evaluated.

Data Collection and Questionnaires

Zarit Caregiver Burden Interview (ZCBI) and Short Form 36 were used as data collection tools.

1. Zarit caregiver burden interview (ZCBI): ZCBI was developed by Zarit, Reever, and Bach Peterson in 1980 (11). The questionnaire, which was originally designed with 29 questions, was then revised as a questionnaire of 22 questions. It is a scale used to evaluate the stress and psychological well-being of caregivers. The scale, which can be filled in by the caregivers themselves or by the researcher, determines the impact of caregiving on the individual's life. Turkish-approved ZCBI was published in 2009 by Ozlu et al. The Turkish version consists of 19 items. Each item is scored from 1 to 5 as 1 = never, = rarely, 3 = sometimes, 4 = quite often, and 5 = almost always. Caregiver burden is assessed according to the total score obtained from all responses. Total scores are calculated between 19 and 95 points, and a higher score indicates a higher caregiver burden. A score of 21 or less demonstrates without burden, 22-46 having a light burden, 47-55 having a moderate burden, and 56 or more having a severe load(12).

2. Short form 36: Short Form 36, which provides wide-angle measurement within the quality of life scales, was developed and made available by Rand Corporation in 1992. The form, which was designed as 149 questions in the development phase, was simplified and then converted into a short form as 36 questions by adding psychometric features. The scale consists of 36 items. The questions provide measuring eight dimensions. Physical function, social function, role limitations due to physical functions, role limitations due to emotional problems, mental health, energy/vitality, pain, and general perception of health are evaluated by the scale. Instead of giving only a single total score, the scale provides a total score for each subscale separately. Subscales peruse health between 0 and 100, so 0 expressing poor health, 100 expressing good health (13-14). The reliability and validity study of the Turkish version of SF-36 was performed by Koçyiğit et al. (15).

Stratification Factors

1.Patient-related factors: Patient-related factors were determined as patient age, gender, educational status, comorbidities, cancer type, active chemotherapy treatment, whether or organ metastasis.

2.Caregiver related factors: Caregiver age, education level, intimacy with the patient (spouse, child, sibling, other relatives, friend), comorbidities were evaluated as factors related to the caregiver.

3. Economic conditions: Factors related to the economic status of the caregiver were determined as the location of his home (city center, district, village), whether the caregiver owning a vehicle, the caregiver owned or rented a house.

Statistical Method

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the

data. Categorical measurements were stated as numbers and percentages, and continuous measurements were expressed as mean and standard deviation (median and minimum-maximum where appropriate). Chi-square and Fisher exact certainty diagnostic tests were used to compare categorical parameters. In addition, the Shapiro-Wilk test was used to determine whether or the parameters in the study normally distributed. Mann-Whitney test was used in pairwise comparisons for parameters that did not normally distribute, and the Kruskal Wallis test was used in more than two group analyses. Finally, Spearman correlation tests were used to specify the relationship between Zarit score and SF 36 scale scores. A multiple linear regression model was used to identify the factors affecting the Zarit score. Statistical significance level was acknowledged as 0.05 in all tests.

RESULTS

The characteristics of patients and caregivers are summarized in **Table 1**. In evaluating the caregiver's Zarit score and the patient's PS ($p<0.05$ for all), the caregivers of PS: 1 group patients compared to PS: 0 group patients were found to have a higher Zarit caregiver burden score. The caregivers of PS: 2 group patients compared to PS: 0 and PS:1 groups were found to have a higher Zarit caregiver burden mean. The caregivers of PS: 3 group patients compared to PS: 0, PS:1 and PS:2 groups were found to have a higher Zarit caregiver burden mean.

Table 1. Patient characteristics, Zarit caregiver burden scores, Short Form 36 scores

	Frequency (n)	Percent (%)
Patients Gender		
Female	172	41.8
Male	239	58.2
Cancer Type		
Lung	65	15.8
Bladder	6	1.5
Thyroid	31	7.5
Melanoma	8	1.9
Pancreas	10	2.4
Brain	11	2.7
Testis	4	1.0
Sarcoma	9	2.2
Head and Neck	9	2.2
Others	30	7.3
Breast	51	12.4
Prostate	43	10.5
Colorectal	58	14.1
Stomach	39	9.5
Kidney	10	2.4
Uterine	8	1.9
Cervix	7	1.7
Ovarian	12	2.9
Patient Comorbidity		
Unavailable	224	54.5
Available	187	45.5
Ecog PS		
0	13	3.2
1	177	43.1
2	172	41.8
3	49	11.9
Organ Metastasis		
Unavailable	261	63.5
Available	150	36.5
Chemotherapy		
Unavailable	247	60.1
Available	164	39.9
Patients Education		
Illiterate	19	4.6
Literate	121	29.4
Primary School Education	162	39.4
High School and Above	109	26.5
Caregiver transportation		
Public Transport	169	41.1
Special Vehicle	242	58.9
Caregiver Place of Residence		
Village, District	162	39.4
City Centre	249	60.6
Cargiver Residence Status		
Tenant	159	38.7
Own House	252	61.3
Caregiver İntimacy		
Spouse	200	48.7
Son	95	23.1
Sibling	53	12.9
Relative	63	15.3
Caregiver Gender		
Female	208	50.6
Male	203	49.4
Caregiver Education		
Literate	108	26.2
Primary School Education	182	44.3
High School and Above	121	29.5
Caregiver Comorbidity		
Unavailable	274	66.7
Available	137	33.3
Zarit Carrgiver Load Weight		
None	9	2.2
Light Load	188	45.7
Medium Load	111	27.0
Heavy Load	103	25.1
	Mean±sd	**Med (Min-Max)**
Patients Age	58.4±13.5	61 (21-92)
Caregivers Age	51.3±10.6	53 (24-70)
Zarit Score	46.7±14.0	48 (20-79)
SF36 Physical function	45.9±10.8	48 (20-77)
SF36 Physical Role Difficulty	45.4±11.0	47 (12-69)
SF36 Pain	46.7±9.0	48 (22-67)
SF36 General Health	47.6±8.9	48 (24-70)
SF36 Energy /Vitality	45.6±7.9	46 (23-73)
SF36 Social Functionality	53.5±9.2	54 (24-77)
SF36 Emotional Role Difficulty	48.8±11.6	51 (20-71)
SF36 Mental Healt	52.3±8.6	52 (24-70)

It was determined that the Zarit score differed according to the patient's education level. It was understood that the difference was due to those with a high school or higher graduation had lower scores than those who uneducated, literate, and had primary education (p<0.05for all). There was no significant difference between the other groups (p>0,05 for all).

There was no significant relationship between caregiver education level and Zarit caregiver burden(p=0.347).

In addition, the caregivers who looked after patients who aged 61 and above, male, with additional comorbidities, with organ metastases, receiving chemotherapy and the caregivers who used public transportation, dwelt in villages or towns, became tenants, had comorbidities, were male were found to have higher Zarit scores (p<0.005 for all)

According to Bonferroni & Tamhane's test, which was performed to detect the cause of the significant difference in the assessment of the Zarit score in terms of the intimacy between patient and caregiver, it was determined that the caregiver who was the patient's child had a higher score than the spouse who was the caregiver (p<0.05). (**Table 2**)

Table 2 . Factors affecting Zarit caregiver burden score

		Zarit			
		Med (Min-Max)			**Med (Min-Max)**
Patients Gender			Cargiver Residence Status		
Female		42 (20-75)	Rent		51 (20-79)
Male		51 (20-79)	Own House		42 (20-78)
	u	-5,947		u	-6,024
	p	<0,001		p	<0,001
Age			Caregiver Gender		
61 <		48 (20-79)	Female		45 (20-79)
61 ≥		47 (20-78)	Male		48 (20-78)
	u	-3,017		u	-6,024
	p	0,003		p	<0,001
PatientComorbidity			Caregiver Comorbidity		
Unavailable		43 (20-77)	Unavailable		44 (20-78)
Available		50 (20-79)	Available		51 (20-79)
	u	-5,514		u	-5,055
	p	<0,001		p	<0,001
Organ Metastasis			Caregiver Place of Residence		
Unavailable		38 (20-76)	Village, County		50,5 (20-79)
Available		58 (33-79)	Town Centre		43 (20-77)
	u	-13,220		u	-5,366
	p	<0,001		p	<0,001
Chemotherapy			Caregiver Transportation		
Unavailable		38 (20-78)	Public Transport		52 (20-79)
Available		54,5 (22-79)	Special Vehicle		41 (20-78)
	u	-12,051		u	-7,316
	p	<0,001		p	<0,001
ECOG PS			Caregiver İntimacy		
0 (a)		22 (20-44)	Spouse (a)		43 (20-78)
1 (b)		37 (21-63)	Son (b)		51 (20-78)
2 (c)		51 (22-76)	Sibling (c)		46 (20-77)
3 (d)		68 (49-79)	Relative (d)		47,5 (22-79)
	z	222,914		z	12,342
	p	<0,001		p	0,006
Bonferroni & Tamhane's T2 p			Bonferroni & Tamhane's T2 p		b-a; p=0,015
		b-a; p<0,001	Caregiver Education		
		c-a; p<0,001	Reading and writing (b)		48 (20-77)
		c-b; p<0,001	Primary Education (c)		50 (20-79)
		d-a; p<0,001	High School and Above (d)		47 (20-78)
		d-b; p<0,001		z	3,304
		d-c; p<0,001		p	0,347
Patients Education			Bonferroni & Tamhane's T2 p		No Difference
None (a)		59 (26-78)			
Reading and writing (b)		48 (22-78)			
Primary Education (c)		47,5 (20-79)			
High School and Above(d)		42,5 (20-75)			
	z	17,885			
	p	<0,001			
Bonferroni & Tamhane's T2 p					
		a-d; p<0,001			
		b-d; p=0,006			
		c-d; p=0,017			

The parameters found significant in assessing by the Zarit score and pairwise and more group analyses were researched via multivariate linear regression analysis (ENTER method). There was a statistically significant correlation between ECOG PS (p<0.001), transportation (p=0.018), residence status (p:0.004), receiving chemotherapy (p<0.001), having a metastatic disease (p:<0.001) and the Zarit score (p<0.05 for all) (**Table 3**).

Statistically significant differences were found between the Zarit caregiver burden groups when the caregivers' Zarit load levels were assessed by SF 36 physical function and SF 36 physical role difficulty, SF 36 pain, SF 36 general health, SF 36 energy/vitality, SF 36 social functionality, SF 36 emotion, SF 36 mental health. Bonferroni & Tamhane's test was performed to determine which subgroups caused the statistical difference between the groups. According to the test results, the source of the difference between caregivers' Zarit load level and SF 36 general health, SF 36 energy/vitality, SF 36 social functionality, and SF 36 mental health scale scores; was determined that the caregivers without a load compared to the load level is medium and heavy, those with a light load level compared to with a medium and heavy load level, those with a medium load level compared to with a heavy load level had higher scores (p<0.05).

Table 3. Zarit score linear regression analysis

	Non-Standardized Coefficients		Standardized Coefficients	t	p
	Beta	sd	Beta		
Patient Comorbidity	0.555	0.558	0.020	0.995	0.320
Ecog PS	2.527	0.548	0.131	4.614	<0.001
Organ Metastasis	8.482	0.676	0.641	6.505	<0.001
Chemotherapy	3.486	0.746	0.236	5.752	<0.001
Patients Education	-0.454	0.306	-0.028	-1.485	0.138
Caregiver Transportation	-0.150	0.075	-0.116	-1.985	0.018
Caregiver Place of Residence	-0.141	0.551	-0.005	-0.256	0.798
Cargiver Residence Status	1.472	0.569	0.960	2.829	0.004
Caregiver İntimacy	-0.300	0.238	-0.024	-1.259	0.209
Caregiver Gender	-0.014	0.544	-0.001	-0.026	0.979
Caregiver Comorbidity	-0.188	0.602	-0.006	-0.313	0.755

The cause of the difference between the groups assessing by Zarit load level and SF 36 physical function, SF 36 physical role difficulty scores; was observed that caregivers without burden compared to caregivers with a medium and heavy load, caregivers with light load levels compared to with a medium and heavy load had higher scores (p<0.05).

According to the SF 36 pain scale, it was stated that caregivers without a load compared to caregivers with a high load level, caregivers with a light load level compared to with a medium and heavy load level had higher scores (p<0.05).

Assessing of SF 36 emotional role difficulty scale, it was expressed that caregivers without a load compared to caregivers with a high load level, caregivers with a light load level compared to with a medium and heavy load level, caregivers with a medium load level compared to with a heavy load level had higher scores (p<0.05) (**Table 4**).

Table 4. Effects of Zarit caregiver burden score on Short Form 36

	SF36 Physical Function	SF36 Physical Role Difficulty	SF36 Pain	SF36 General Health	SF36 Energy / Vitality	SF36 Social Functionality	SF36 Emotional Role Difficulty	SF36 Mental Health
	Med (Min-Maks)	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)	Med (Min-Max)
Zarit Carrgiver Load Weight								
None (a)	54 (46-77)	56 (44-68)	56 (41-65)	57 (40-70)	51 (40-73)	59 (49-77)	59 (39-64)	63 (50-66)
Light Load (b)	51 (34-69)	51 (30-69)	51 (33-67)	52 (36-70)	50 (37-68)	57 (34-77)	55 (23-71)	57 (40-70)
Medium Load (c)	48 (24-63)	47 (20-63)	48 (26-62)	47 (25-63)	45 (24-54)	54 (26-69)	51 (22-70)	52 (26-67)
Heavy Load (d)	32 (20-50)	31 (12-58)	38 (22-59)	38 (24-60)	39 (23-53)	48 (24-65)	35 (20-58)	45 (24-60)
z	237,076	213,157	167,927	176,735	182,133	134,568	154,950	123,622
p	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001
Bonferroni & Tamhane's T2 p								
	a-c; p<0,001	a-c; p=0,001	a-d; p<0,001	a-c; p=0,011	a-c; p=0,002	a-c; p=0,002	a-d; p<0,001	a-c; p=0,017
	a-d; p<0,001	a-d; p<0,001	b-c; p<0,001	a-d; p<0,001	a-d; p<0,001	a-d; p<0,001	b-c; p<0,001	a-d; p<0,001
	b-c; p<0,001	b-c; p<0,001	b-d; p<0,001	b-c; p<0,001	b-c; p<0,001	b-c; p<0,001	b-d; p<0,001	b-c; p=0,001
	b-d; p<0,001	b-d; p<0,001		b-d; p<0,001	b-d; p<0,001	b-d; p<0,001	c-d; p<0,001	b-d; p<0,001
				c-d; p<0,001	c-d; p<0,001	c-d; p<0,001		c-d; p<0,001

A moderate reverse relationship was detected between Zarit scores of caregiver s and scale scores of SF36 physical function (r=-0.744), SF 36 physical role difficulty (r=-0.697), SF 36 pain (r=-0.604), SF 36 general health (r=-0.624), SF 36 energy /vitality (r=-0.635), SF 36 social functionality (r=-0.545), SF 36 emotional role difficulty (r=-0.575), SF 36 mental health (r=-0.535) (p<0.05) (**Table 5**).

Table 5. Zarit caregiver burden and Short form 36 correlation

	Zarit	
	r	p
SF36Physical function	-0,744**	<0,001
SF36Physical Role Difficulty	-0,697	<0,001
Sf36 Pain	-0,604	<0,001
SF36General Health	-0,624	<0,001
SF36Energy /Vitality	-0,635	<0,001
SF36Social Functionality	-0,545	<0,001
SF36Emotional Role Difficulty	-0,575	<0,001
SF36 Mental Healt	-0,535	<0,001

* p<0,05, Spearman correlation test

DISCUSSION

A multiple evaluation strategy was applied in our study. The effects of the clinical characteristics of 411 patients who were followed up and treated in our hospital's oncology polyclinics between January 2020 and March 2021 and the social status of their caregivers on Zarit caregiver burden were perused. In addition, the effects of Zarit caregiver burden on the short form 36, which indicates the quality of life of the caregiver, were researched.

It was confirmed that PS, patient education level, age, gender, having additional comorbidity, having metastatic disease, receiving chemotherapy, using public transportation, village or district residence, becoming tenants, gender were associated with high Zarit caregiver score in our study (p<0.05 for all).

It was detected that PS, using public transportation, becoming tenant, receiving chemotherapy, having metastatic disease were associated with a high Zarit caregiver burden score in the multivariate linear regression analysis (p<0.05 for all).

It was determined that when the Zarit caregiver burden score increase, SF 36 scores of the caregiver's quality of life scale score decrease (p<0.05 for all).

The rise in chronic diseases with the aging population and the promising treatment methods that have emerged in the last century in treating chronic diseases reveals a patient population in need of long-term care. The patient group with cancer has an essential part in this population. Some of the patients are influenced in a wide range from physical independence to complete dependence because of the physical effect of cancer on patients and/or the life quality impairment in patients receiving cancer treatment. The majority of patients need continuous daily care. Unfortunately, this need is often met by family members or close friends who do not have the qualifications and training in care for the vast majority. While people who undertake caring for patients struggle with problems they have no experience with, they endeavor to go on their lives to cope with their health problems and stress. Difficulty in dealing with more than one problem makes caregivers feel insufficient, so this situation negatively affects the caregiver's quality of life as much as the patient (16,17).

One of the quick and elementary indicators of whether or the patient can survive without support is the performance score evaluation. It was reported that caregivers of patients with PS:3-4 had a statistically significantly higher Zarit caregiver burden score compared to caregivers of patients with PS:0-2 in a study of patients with lung cancer about performance score (PS) and Zarit caregiver burden by Wood et al. (18) (p:0.008). It was stated that high Zarit caregiver burden scores were observed in caregivers of patients with high-performance scores in the study on 441 cancer patients aged 60-80 years by Semere et al. (19). It was revealed that poor performance score was a factor predicting high Zarit caregiver burden in the study on patients with brain tumors by Bayen et al. (20). PS was demonstrated as one of the main factors affecting Zarit caregiver burden in line with the general literature in multivariate linear regression analysis in our study(p<0.005).

Studies focusing on cancer's financial burden on the caregiverr express a heavy economic burden on the patient and their caregivers, additionally the physical and psychological burden. It was demonstrated that informal caregiver expenditure costs $4563 for each patient per three-month average; however, this expense was not less than nursing homes and official patient care institutions in a study on cancer patients by Stommel et al. (21). It was found that total informal expenditure was average out $7,290 for three months, and caregivers of patients in the last six months of their lives had more expense in another study that specifically examined the costs of adult cancer care (22). The annual cost of the disease to caregivers was estimated as 7,028, 19,701, and 14,234 dollars in the first year, after the first year, and in the terminal period, respectively, in a study on caregivers of patients with colorectal and lung cancer by Van Houtven et al. (23). Longo et al. also reported that 20% of cancer patients' caregivers experience significant financial problems (24). We speculated that patients and caregivers with low socioeconomic status would be exposed to higher

caregiver burden due to the additional financial burden. Consequently, it was determined that parameters that were questioned and taken as indicators of low economic status in our study, such as using public transportation and becoming tenant, were associated with a higher caregiver burden (p<0,05 for all).

The physical and psychological conditions of cancer patients become worse, usually during chemotherapy treatment. When the duration of chemotherapy increases, it is possible to develop functional impairment due to emerged and increased adverse effects (25). Correlatively, it has been reported that caregivers of cancer patients experience intense mental problems during the diagnosis and treatment of cancer, and social functionality is negatively affected (26). It was specified that caregivers have difficulties managing adverse effects and have concerns about the effectiveness of the treatment during the cancer treatment of patients in the study performed by Northouse et al. (27). Inadequacy coping skills because of the adverse effects of developing in patients during chemotherapy and the difficulties managing these adverse effects may explain having more significant caregivers' burden during chemotherapy (28). Our study showed that caregivers of patients receiving active chemotherapy treatment had higher Zarit caregiver burden scores than caregivers of cancer patients who were not receiving chemotherapy treatment (p<0.05).

Metastatic cancer patients may have many difficult to manage symptoms; besides, these patients are likely to receive aggressive treatments and are often exposed to a considerable amount of treatment-related adverse effects (29). It has been shown that caregivers of metastatic cancer patients have more intensive anxiety symptoms by some authors (30-31). It was demonstrated that caregivers of patients with relapsed and metastatic disease have more distress, strain, and compliance problems than caregivers of patients with early-stage disease in a study performed by Morse et al. (32). The findings in our research that caregivers of metastatic cancer patients had a higher Zarit caregiver score than caregivers of patients without metastases supports these results (p<0.05).

Many studies have focused on the life quality of cancer patients during diagnosis and treatment. The studies about the life quality of cancer patients' caregiver s are relatively limited in the literature (33,34). The lower SF36 scores were obtained from the caregivers included in the study in mental health, vitality, and social functioning subgroups compared to the normal population in a study performed on 96 individuals caring for cancer patients by Grov et al. (35). It was determined that pain and mental role were the most affected SF-36 subscales in a study on caregivers of patients with hematological malignancies by Gereklioglu et al. (36). Our study is the first to compare Zarit caregiver burden score with SF-36 scores on caregivers of cancer patients in the literature review. Our results represent that SF-36 scores, one of the life quality scales, decrease in conjunction with Zarit caregiver burden increases in caregivers. There is a moderate reverse relationship between Zarit scores and SF36 subscales. It can be deduced from the results of our study that social support services for patients and their caregivers should be used more effectively and intensively to maintain the well-being of the patient, although the state pays for oncological treatments in many countries

There are some limitations in our study. The most important limitations of our study are that it was conducted in a single-center, cross-sectional, and limited population, which is a homogeneous community with a specific culture. However, we think our study as the first study to compare the Zarit caregiver burden questionnaire and the SF-36 questionnaire on caregivers will contribute to the literatüre..

CONCLUSION

Nowadays, only disease-oriented medicine practices are unfortunately insufficient to evaluate the patient's well-being in a physically, psychologically, socially, and economically devastating disease such as cancer. Inadequate social support usually causes treatment incompatibility, which means shorter disease-free and overall survival for patients. Therefore, we think that the caregivers of cancer patients are also an essential factor that should be considered in terms of the patient's well-being and treatment compliance. Our study reveals the need to peruse the patient with the caregiver as a whole, although caregivers are ignored during medical practices. Zarit caregiver burden scores are influenced by the patient's clinical characteristics and the caregiver's social and economic status. The increased Zarit caregiver burden negatively affects the caregiver's life quality.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study received approval from the Institutional Review Board of Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (Date 09.06.2021; Decision No: 829).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Evaluation of hospital acquired infections in the tertiary intensive care unit: a three-year analysis

Fatma Yılmaz Aydın[1], Emre Aydın[2]

[1]Dicle University, Faculty of Medicine, Department of Internal Medicine, Diyarbakır, Turkey
[2]Dicle University, Faculty of Medicine, Department of Nephrology, Diyarbakır, Turkey

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ABSTRACT

Introduction: Hospital-acquired infections (HAI) occurring in intensive care units (ICUs) are an important risk factor for mortality and morbidity. In some patient groups followed in ICUs, the risk of developing nosocomial infections increases even more. Especially, patients with end-stage renal disease (ESRD) carry a serious risk for HAI when they are hospitalized in ICUs. Our aim is to determine the rate and incidence of hospital infection, the distribution of infections and the most common microorganisms in our ICU, to initiate appropriate empirical treatment and to prevent the development of antibiotic resistance.

Material and Method: A total 158 patients with a diagnosis of hospital-acquired infection hospitalized between January 2017 and December 2019 at general internal medicine intensive care unit, were included in this study. The clinical findings, culture results and laboratory data of the patients were recorded. According to years, the HAI rate, density and infection agents in the ICU were determined.

Results: 158 episodes of nosocomial infections were detected in 128 of 556 patients who were hospitalized within three years. The hospitalization day was 9048, and the three-year ICU HAI rate was calculated as 29.19%. HAI density was 17.45 in 1000 patient days. Bloodstream infection was the most common (30.38%), followed by ventilator-associated pneumonia (28.48%) and catheter-related urinary tract infection (24.68%). Gram-negative microorganisms were the most common infectious agents. Among the Gram-negative bacteria, the most frequently isolated bacteria were *A. baumannii, K. pneumoniae* and *P. aeruginosa*. Among Gram-positive bacteria, *Enterococcus* spp. was most frequently isolated

Conclusion: The risk of HAI is high in patients hospitalized in ICUs. In order to control nosocomial infections, HAI incidences and rates should be evaluated, infectious agents, and prospective effective infection control strategies should be developed by taking necessary precautions according to surveillance results. These measures will significantly reduce the incidence of HAI.

Keywords: Intensive care units, hospital infections, gram negative bacteria, central venous catheter, urinary tract, catheter related infections, infection control

INTRODUCTION

Hospital-acquired infections (HAI) are defined as infections that develop 48-72 hours after hospital admission or within 10 days after discharge, in which the patient does not have any infection before admission to the hospital or in the first days of hospitalization (1). HAI occurring in intensive care units (ICUs) are an important risk factor for mortality and morbidity. The incidence of hospital-acquired infections is 2-5 times higher in ICUs than in clinical services. (2). The reasons for this, we can count the patient-related comorbidities such as long hospital stays in ICUs, perform of many invasive procedures, cross contamination and diabetes mellitus, kidney failure, heart failure, and liver failure (3). In some patient groups followed in ICUs, the risk of developing nosocomial infections increases even more. Especially, patients with end-stage renal disease (ESRD) carry a serious risk for HAI when they are hospitalized in ICUs. It is known that these patients have additional comorbid conditions, invasive vascular procedures used for Renal Replacement Therapy (RRT), uremic toxicity and anemia increase the susceptibility to hospital-acquired infections (4).

Hospital infection rates and incidence, foci of infection, causative microorganisms and antibiotic resistance may differ between different ICUs of the same hospital. It is very important for each unit to know its own flora

Corresponding Author: Fatma Yılmaz Aydın, fatmay83@hotmail.com
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and antibiotic resistance, in order to determine the infection control measures to be taken in these units and the appropriate empirical antibiotic therapy. In this study, the epidemiological characteristics of HAIs in the Internal Medicine ICU and their change over the years were investigated. Our aim is to determine the rate and incidence of hospital infection, the distribution of infections by regions and the most common microorganisms in our ICU, to initiate appropriate empirical treatment and to prevent the development of antibiotic resistance.

MATERIAL AND METHOD

Approval for the study was granted by the Ethics Committee of Dicle University Faculty of Medicine (Date: 06.02.2020, Decision No: 144). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between January 2017 and December 2019, 556 patients were hospitalized in the general internal medicine intensive care unit. The information of these patients was analyzed retrospectively. Among these patients, regardless of gender, 158 patients aged over 18 years and followed up in the intensive care unit for at least 72 hours, were diagnosed with HAI and included in the study. Patients' HAIs are followed by an active, prospective surveillance study based on patient and laboratory, by infection control doctors and nurses five days a week. This information is recorded daily in the surveillance network. Infections occurring 48 hours after admission to the ICU, but not before or during admission, were defined as HAI. Diagnoses of ventilator-associated pneumonia, catheter-associated urinary tract infection, laboratory-confirmed bloodstream infection, and central venous catheter (CVC) related infection were defined according to Centers for Disease Control and Prevention (CDC) guidelines. (5) In the diagnosis of HAI, peripheral blood as a laboratory finding; leukocyte, platelet count, C-reactive protein (CRP) value, in urine analysis; pyuria and nitrite positivity, radiologically; detection of new infiltration in the lungs, as a clinical finding; parameters such as fever, lung aural finding, hypotension, dysuria and suprapubic tenderness were used. At the time of diagnosis of HAI, clinical and laboratory findings were examined. Cultures of the areas thought to be the focus of infection (urine, sputum, wound site, catheter, and deep endotracheal aspirate from those who received ventilator therapy) were taken from all patients who were thought to have HAI. BACTEC peds plus/F (BD,Sparks, MD)® culture bottles were used for blood samples. Identification of the microorganism and determination of antibiotic susceptibility were performed using the automated Phoenix culture system in line with the recommendations of the Clinical and Laboratory Standards Institute in the USA. The clinical findings, culture results, radiological and laboratory data of the patients diagnosed with HAI were recorded in the prepared standard form. HAI rate and incidence density were calculated. (HAI rate (%) = Number of HAI/number of patients admitted x 100, Incidence density= Number of HAI/patient days x 1000). According to these data, the HAI rate and infection factors in the ICU were determined.

RESULTS

158 episodes of nosocomial infections were detected in 128 of 556 patients who were hospitalized in the General Internal Medicine ICU between January 2017 and December 2019 and followed up for at least 72 hours. The mean age of 128 patients diagnosed with HAI was 49.6 (18-89). 43% (n:55) of the patients were female and 57% (n:73) were male. The hospitalization day was 9048, and the three-year ICU HAI rate was calculated as 29.19%. The incidence of HAI by years was 51.7%, 33.1% and 11.36%, respectively. HAI density was 17.45 in 1000 patient days. The distribution of hospital-acquired infection rate by years is shown in **Table 1**.

Table 1. The number of patients, hospital days, the number of patients who developed HAI, the number of HAI, the rate and density of HAI in the General Internal Medicine ICU between 2017-2019

Year	Number of inpatients	Hospitalization day	Number of patients who developed HAI	HAI rate	HAI density
2017	159	2900	82	51.57	28.28
2018	142	3086	47	33.1	15.23
2019	255	3062	29	11.36	9.47
Total	556	9048	158	29.19	17.45

When we analyzed the three-year invasive device-associated infection data, the rate of mechanical ventilator use in ICU patients was 0.65, the day of use was 3908, and the rate of VAP (ventilator associated pneumonia) was 10.24%. The rate of urinary catheter use was 0.99, the day of use was 8953, and the rate of catheter-related urinary tract infection was 4.36%. The CVC usage rate was 0.8, the day of use was 7214, and the CVC-related bloodstream infection rate was 3.05%.

When the distribution of HAI attacks was examined, bloodstream infection was the first and pneumonia was the second (**Table 2**). When analyzed by years, the most common cause of infection was catheter-related urinary tract infection in 2017, pneumonia in 2018, and CVC-related bloodstream infection in 2019. In addition, when we analyzed HD patients by years, we found that the most common CVC-related bloodstream infection developed in these patients for three years.

Table 2. Distribution of hospital acquired infections according to the infection sites

Type of HAI	Number of infections	Percent of total infections	HAI rate	HAI dansite
Bloodstream infection	48	30.38	8.87	5.31
Ventilator-associated pneumonia	45	28.48	8.32	4.97
Urinary catheter related infection	39	24.68	7.20	4.31
Central venous catheter associated bloodstream infection	22	13.92	4.07	2.43
Skin and soft tissue infection	4	2.53	0.74	0.44
Total	158	100	29.19	17.45

Gram-negative microorganisms were frequently isolated as infectious agents in our ICU. Among the Gram-negative bacteria, the most frequently isolated bacteria were *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*. Among Gram-positive bacteria, *Enterococcus* spp. was most frequently isolated (**Figure 1**). When the foci of infection were examined, *Klebsiella* spp. in bloodstream infections, *Acinetobacter* spp. in VAP, *Klebsiella* spp. in urinary catheter-related infections, *Klebsiella* spp. and *Acinetobacter* spp. in CVC-related infections were found to be the most common agents. When the antibiotic susceptibility was examined, the most effective antibiotic in *A. baumannii* that is the most frequent microorganism, was colistin, while its sensitivity was 75.09% for three years. The most effective antibiotics against other Gr (-) microorganisms were amikacin, imipenem, and meropenem, while linezolid and vancomycin were effective against Gr (+) microorganisms.

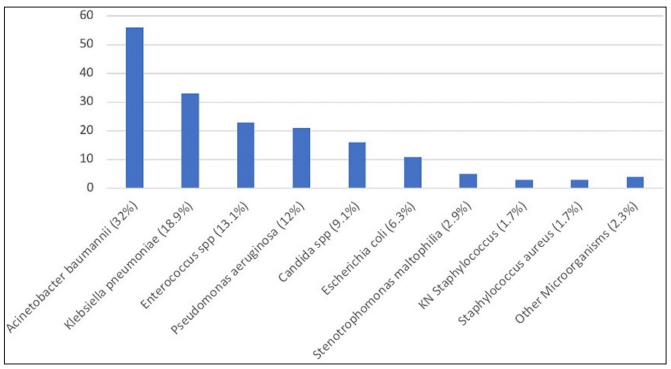

Figure 1. Microorganisms isolated from patients with positive culture

DISCUSSION

ICUs are units that have many risk factors for the development of HAI, and where invasive procedures such as mechanical ventilator, tracheostomy and catheter are frequently performed. The most important factors that increase the risk of HAI are factors belonging to the patient, invasive procedures, and cross contamination. As the number of invasive procedures increases, the number of mechanical ventilation-associated pneumonia, catheter-related urinary tract infections and CVC-related bloodstream infections increase in parallel. HAI is an important cause of mortality and morbidity for patients followed in the ICU. Therefore, it is important to determine HAI agents and their antibiotic susceptibility in terms of reducing mortality and morbidity.

In different studies conducted in our country, it has been reported that the rate of HAI is between 5.3-64.6%, although it varies according to ICUs (6). When studies on nosocomial infections in the literature were scanned, the rate of HAI was found to be 34.5% in a prevalence study in which 1150 ICUs from 88 countries participated (7). In their three-year analysis, Taş et al. (8) found the highest HAI rate to be 34.31% and the lowest to be 13.14%. In another study, 5204 intensive care patients were screened, and 269 nosocomial infections were detected. In this study, the HAI rate was calculated as 27.3% (9). In our study, we found the HAI rate to be 29.19% on average, although it decreased over the years. The reason for the low rate of HAI over the years can be counted as active surveillance, attention to isolation measures, especially standard precautions, and the continuity of the education to raise awareness of all staff on this issue. The density of HAI is as important as its rate. In studies conducted in our country, HAI density varies between 15.4 and 44.7 (10). Cetin et al. (11) found the HAI density of 21.9 in their two-year analysis of patients hospitalized in the ICU. In our study, we found the HAI density as 17.45. Our results are compatible with the literature.

Invasive devices increase the risk of nosocomial infection because it disrupts the barrier integrity of the body, facilitates the formation of biofilm, and can cause infection with less bacteria as well as strains with low virulence (10). The widespread use of intravascular catheters in ICUs is one of the most important factors contributing to the development of catheter-related infections. Especially CVCs are the most common types of catheters that can cause these infections (3). When we examine the rate of invasive catheter-related infections and catheter use rates in the literature, according to the National Health Service-Related Infections Surveillance Network of our country's Ministry of Health 2020 data, the rate of mechanical ventilator use in internal medicine ICUs in all university hospitals is 0.46, the rate of VAP is 8.3%, the rate of urinary catheter use is 0.95, the rate of catheter-related urinary tract infection is 1.3%, the rate of CVC use is 0.71, the rate of CVC-related bloodstream infection is 3.1% (12). Sahin et al. (10) found that the rate of VAP in the neurology ICU was 12.4%, the rate of catheter-related urinary tract infection was 2.53%, and the rate of CVC-related bloodstream infection was 5.14%. In another study that included internal and surgical ICUs, the infection rate was found to be 0.39 in

patients diagnosed with catheter-related urinary tract infection (13). According to our findings, the rate of mechanical ventilator use is 0.65 and the rate of VAP is 10.24%. The rate of urinary catheter use was 0.99, and the rate of catheter-related urinary tract infection was 4.36%. CVC usage rate was 0.8, CVC-related bloodstream infection rate was 3.05%. The reason why our VAP rate is higher than our country's data can be attributed to the higher ventilator usage rate. Our rate of CVC-related bloodstream infection is similar to the data of our country.

Nosocomial infections in ICUs often develop in areas such as the respiratory tract, abdomen, catheter-related bloodstream, urinary system, skin-soft tissue, and central nervous system. Vincent et al. (7) showed in the prevalence study that the most common infections were pneumonia and bloodstream infections. In the study of Taş et al. (8) urinary system infections were the first, while bloodstream infections were the second. In another study, while ventilator-associated pneumonia was the most common HAI, it was followed by central venous catheter-related bloodstream infection (9). In our study, bloodstream infection was the first, while pneumonia was the second. In addition, when we analyzed the infection foci by years, the most common infection foci were catheter-related urinary tract infection in 2017, pneumonia in 2018, and central venous catheter-related bloodstream infection in 2019.

Nosocomial infections are common in hemodialysis patients followed in ICUs. Catheters used especially for RRT constitute an important risk factor for HAI. It is also known that uremia causes immune dysfunction and increases susceptibility to infection (14). In a study examining nosocomial infections in HD patients, urinary catheter-related infection was the most common, followed by catheter-related bloodstream infection and pneumonia (4). In another study in which 110 cases were evaluated, pneumonia, catheter-related bloodstream infections and urinary catheter-related infections were found to be the most common, respectively (15). In our study, the most common central venous catheter-related bloodstream infection was seen in patients undergoing HD.

HAI rates with Gram-negative bacteria, which do not cause infection in healthy individuals but are frequently encountered in ICUs, have increased in recent years (3,8,9,11). When the distribution of causative microorganisms in HAIs in our country is examined, *Klebsiella* spp. in bloodstream infections, *Acinetobacter* spp. in VAP, *Klebsiella* spp. in urinary catheter-related infections, and *Klebsiella* spp. and *Acinetobacter* spp. in central venous catheter-related bloodstream infections are the most common agents (16). Şahin et al. found that *Acinetobacter* spp. in VAP and *Klebsiella* spp. and *E. coli* in catheter-related urinary tract infections were the most common agents in their study (10). In a multicenter study, culture results were examined, and Gram (-) microorganisms were detected with 70.7% (*Klebsiella* spp., *E. coli*, *Pseudomonas* and *Acinetobacter*, respectively). Also in the same study, when the agents were evaluated according to the foci of infection, the most frequently isolated microorganisms were *Klebsiella* spp. and *Acinetobacter* spp. in respiratory tract, *Klebsiella* spp. in bloodstream infections, *E. coli* and *Klebsiella* spp. in urinary system infections (7). When the literature is evaluated, it is seen that *Acinetobacter* spp. and *Klebsiella* spp. are in the first place, as in our study. *Candida* species are another cause of blood infections that are accepted as hospital infections in intensive care units. In studies performed, *Candida* species have been reported as an infectious agent in 8-15% of ICUs (3). We found the rate of *Candida* spp as 9.1% in our study.

The main limitation of our study is the fact that it is a retrospective study with a relatively small sample size, single center, and single ICU. Studies with more comprehensive analyses and a larger number of patients can provide further data on these variables.

CONCLUSION

The risk of HAI is high in patients hospitalized in ICUs. Mortality and morbidity increase in patients who develop nosocomial infections, and the length of hospital stay is prolonged. In order to control nosocomial infections, HAI incidences and rates should be evaluated, infectious agents and resistance profiles should be regularly monitored, and prospective effective infection control strategies should be developed by taking necessary precautions according to surveillance results. Taking these precautions plays an important role in reducing mortality and morbidity.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Dicle University Faculty of Medicine (Date: 06.02.2020, Decision No: 144).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Using the fractal dimension method to assess ossification after open sinus lift surgery

Bahadır Sancar[1], Numan Dedeoğlu[2], Yunus Çetiner[1], Cüneyt Asım Aral[3], Oğuzhan Altun[2]

[1]İnönü University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Malatya, Turkey
[2]İnönü University, Faculty of Dentistry, Department of Oral and Maxillofacial Radiology, Malatya, Turkey
[3]İnönü University, Faculty of Dentistry, Department of Periodontology, Malatya, Turkey

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ABSTRACT

Objective: The present study aims to use the fractal dimension method to assess ossification occurring in patients undergoing an open sinus lift surgery performed with the use of xenograft.

Material and Method: In our study, we used 90 orthopantomographs of a total of 43 patients. Our study consists of three groups: Group A, Group B, and Group C. Using the fractal dimension method, we assessed the orthopantomographs taken within three to six months after the open sinus lift surgery (Group A), taken after six to nine months after the open sinus lift surgery (Group B), and taken more than nine months after the open sinus lift surgery (Group C). The data were analyzed using IBM SPSS V23. The compliance of the data with the normal distribution was examined using the Shapiro-Wilk test.

Result: The three-way statistics made between the mean values of the groups revealed a difference (p=0,033). The density of the xenograft material in the study area tended to decrease starting from the period of three to six months after the surgery.

Conclusion: The fractal dimension method can be used to assess ossification occurring after open sinus lift surgery that is performed with the use of xenografts.

Keywords: Fractal dimension/open sinus lift/xenograft

INTRODUCTION

Dental implant treatment is an effective option for the replacement of lost teeth and for the retention and stability of removable dentures and maxillofacial prostheses. The alveolar bones of the jaws undergo continuous resorption after tooth loss (1). After the extraction of teeth, the alveolar resorption in the posterior maxilla and the increasing pneumatization of the maxillary sinus limit the amount and quality of bone needed for implant placement in this region (2,3). Although the usage of short or curved implants has been indicated as a viable therapeutic option to overcome these obstacles (4), sinus grafting emerges as a good option to facilitate implant placement, considering the anatomical constraints and the long-term biomechanical stability of the prosthesis (3). Therefore, a variety of methods have been needed to obtain the necessary bone structure in the sinus region. Among the sinus augmentation procedures, the techniques of the lateral window and sinus floor elevation (performed with an osteotome) have gained recognition in treating the loss of vertical bone height in the posterior maxilla (1).

Bone grafting material is one of the factors that play an important role in sinus grafting outcomes. Xenografts are biocompatible materials that offer a structure and physical characteristics that are similar to human cancellous bone (3). The inorganic bovine bone combined with autogenous bone can be a perfect graft material for maxillary sinus augmentation (5). This can be explained by the slow absorption rate and osteoconductive characteristics of the inorganic xenograft (6).

Many methods have been put forward to examine trabecular structures, however, the most commonly used one today is the fractal dimension (FD) method, and it is indicated with the value of fractal dimension (FD) in numerical terms (7). The word fractal derives from the Latin word fractus, which means fractured (8). For a long time, fractal geometry has been used to identify irregular patterns which exhibit self-similarity at different scales (7). Fractals are especially used in the characterization of a porous medium (9). Again, the fractal analysis method is widely used for image analysis and pattern

Corresponding Author: Bahadır Sancar, bahadir.sancar@inonu.edu.tr **Received:** 24.11.2021 **Accepted:** 04.01.2022

recognition (7), and the spongiform bone exhibits fractal characteristics due to its reticulated structure. Therefore, fractal geometry and fractal dimension measurements can be used to identify the complex structure of trabecular bone (10). The magnified image which monitors the internal porous structure of the bone at different scales resembles the initial original unmagnified appearance (7). Generally, as the size scale increases, the shape gets equally complex (11). It is specified that the FD obtained from orthopantomography indicates the changes in the density of the spongiform bone and the mineral loss in the bone (12).

Bone tissue consists of two parts, cortical and cancellous, and the ratio of these two structures in the entire bone is approximately 80% and 20%, respectively (13). Due to its proximity to the bone marrow cavity, remodeling is more apparent in cancellous bone, which is the most metabolically active component of the skeleton (14). However, cancellous bone is also extremely susceptible to disruptions induced by local or systemic factors that can cause a significant imbalance in bone turnover (14).

In our study, we aimed to assess the grafted area with a fractal analysis of orthopantomographs taken during the postoperative follow-up of the patients who were treated with open sinus lift surgery. This study hypothesizes that fractal analysis can be used to assess ossification occurring in the operated area after open sinus lift operations performed with the use of xenograft. We could not find any other study in the literature using fractal analysis to assess, based on the postoperative periods, the area undergoing open sinus lift surgery.

MATERIAL AND METHOD

This study was carried out at İnönü University Faculty of Dentistry, Department of Oral, Dental, and Maxillofacial Radiology. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In this study, images obtained by using planmeca proline XC (2009, 60-80 kVP, 4-12 mA, 18 second exposure time, Helsinki, Finland) panoramic device were used. In our study, we used 90 orthopantomographs of a total of 43 patients who were treated with open sinus lift surgery between September 2018 and June 2021. Fractal analysis was performed on the orthopantomographs taken three to six months after the surgery (A), six to nine months after the surgery (B), and more than nine months after the surgery (C). The study included patients who were treated with bilateral or unilateral open sinus lift surgery performed with the use of xenograft (Apatos, Osteobiol). The study excluded the patients with systemic problems that would endanger the bone healing process, the patients with severe parafunctional habits, the patients with substance abuse, and the patients with severe periodontal disease. Care was taken not to let any anatomic structures, such as tooth roots, be visible in the images obtained from panoramic radiographs. After determining an area of 20x20 pixels using the most superior region of the graft placed, fractal dimension (FD) analysis was performed in the maxilla using the box-counting method. The operations related to fractal dimension analysis were carried out by the same person on the same computer. Fractal dimension analysis was performed in the ImageJ image analysis software, which is a version of the National Institute of Health Image, using the method developed by White and Rudolph. (15). Fractal dimension analysis operations were performed in the following order: After the relevant area to be examined in the image was cropped, it was saved and copied in the 8-bit format. Then, a Gaussian filter (sigma= 35 pixels) was applied to the duplicated image, and the image was blurred. The image (which was blurred by applying the Gaussian filter) was then subtracted from the original image by the 'subtraction' process. A brightness value of 128 was added to each pixel location. Regardless of the initial brightness of the image, 128 was determined as the threshold value. The image taken as the threshold value was converted to binary format. To avoid redundancy in the image, erosion and dilatation processes were applied to the image. The inverted image was skeletonized, and in this way, it was made sure that only the central parts of the trabeculae remained. In the ImageJ software, FB analysis was performed on the skeletonized image by using the 'box-counting' function.

Statistical Method

The data were analyzed using IBM SPSS V23. The compliance of the data to normal distribution was examined using the Shapiro-Wilk test. To compare the intragroup values that exhibited normal distribution according to gender, the independent two-sample t-test was used. To compare the data that exhibited normal distribution according to groups, the one-way analysis of variance (ANOVA) was used. Also, multiple comparisons were examined with the Tukey HSD test. For quantitative data, the analysis results were presented as mean±standard deviation and median (minimum-maximum). The level of significance was taken as $p < 0.05$.

RESULTS

A significant difference was found between the mean values of the groups ($p=0.033$). The mean value was 0.97 in Group A, 0.96 in Group B, and 0.92 in Group C. While the mean value in Group B did not exhibit any difference compared to Groups A and C, the mean value of Group A was higher than that of Group C (**Table 1**).

Table 1. Comparison of the values according to groups				
Groups	**Number of samples**	**Mean ±S. deviation**	**Median (Min.-max.)**	**p***
A	n=30	0.97±0.09[a]	0.99 (0.85-1.13)	0.033
B	n=30	0.96±0.08[ab]	0.97 (0.81-1.10)	0.033
C	n=30	0.92±0.09[b]	0.92 (0,75-1,09)	0.033
*One-way analysis of variance (ANOVA); [a-b] There is no difference between the groups with the same letter.				

The mean values of Group A did not exhibit a difference according to gender (p=0.445). In Group A, while the mean value for women was 0.97, the mean value for men was 0.99. The mean values obtained in Group B did not exhibit a difference according to gender (p=0.709). In Group B, while the mean value for women was 0.96, the mean value for men was 0.95. The mean values obtained in Group C did not exhibit a difference according to gender (p=0.363). In Group C, while the mean value for women was 0.91, the mean value for men was 0.94 (**Table 2**).

Table 2. Comparison of the data within the groups according to gender			
	Mean±S. deviation	**Median (Min.-Max.)**	**p***
Group A			0.445
Female	0.97±0.09	0.97 (0.85-1.13)	
Male	0.99±0.09	1.01 (0.85-1.1)	
Group B			0.709
Female	0.96±0.08	0.97 (0.82-1.1)	
Male	0.95±0.09	0.98 (0.81-1.07)	
Group C			0.363
Female	0.91±0.09	0,92 (0,75-1,09)	
Male	0.94±0.09	0.93 (0.75-1.07)	
*Independent samples t-test			

DISCUSSION

In our study, we performed the fractal dimension analysis on the orthopantomographs to assess the aftermath of the xenograft material placed in the patients who were treated with open sinus lift surgery, focusing on the period of three to six months from the surgery, on the period of six to nine months from the surgery, and on the period of more than nine months from the surgery. The results obtained in the study verify the hypothesis of the study. Although there was no difference between Group B and Groups A, C, we observed that trabeculation increased as the duration increased.

The histological and histomorphometric techniques can be used to examine the mineral quality of the grafted bone and the structure of the trabecular bone, but the invasive nature of the procedure is disadvantageous (16). In the evaluation of hard tissue and hard tissue grafts, Micro-CT is precise and non-invasive. However, the high amount of x-rays projected onto the patient and its cost are the disadvantages of this method (17). Orthopantomographs are widely used to assess the condition of the grafted bone before dental implants are made. While the non-invasive nature of this X-ray-based technique is an advantage, its capability of providing only low-resolution, two-dimensional images is a disadvantage (18). Some properties of orthopantomographs, such as low radiation emission, low cost, and non-invasiveness, are advantageous for postoperative evaluations.

There are various procedures to gain bone height, and open sinus lift surgery has become a standard procedure to enable the placement of dental implants, especially in the presence of insufficient bone in the posterior maxilla (19). Different graft materials such as autografts, xenografts, alloplastic materials, and the combinations of these materials can be used for this procedure (20, 21). Considering the disadvantages of autogenous bone grafts, non-autogenous graft materials are considered an alternative (22). Xenografts are similar to human cancellous bones in terms of their crystalline and morphological structure (23).

Many studies have been carried out to evaluate bones in terms of their quality (24,25). Most of these studies have used the data related to the mineral density measurement of the bone performed with the Dual-energy X-ray absorptiometry method and the data related to the radiomorphometric measurements called panoramic mandibular index (26). These studies evaluating the density and macrostructure of the bone do not provide sufficient information about the trabecular structure of the bone. However, the trabecular bone plays an important role in the durability of the bone, and together with the cortical bone, it determines the biomechanical properties of the bone (27). In recent years, fractal analysis has gained popularity in terms of the detection of possible abnormalities, the evaluation of existing disorders in bone structure, and the evaluation of changes in the bone structure (28). While a high FD value indicates a more complex and dense bone structure, a low FD value indicates a more porous bone structure (29). Measuring and calculating FD is easy, and the measurement area is determined subjectively. The obtained quantitative values provide objective information regarding the tissue of the bone or regarding the bone-like structure. Several studies have evaluated FD in different ways (28-30). The most frequently used method in the literature to calculate FD is the box-counting technique, which was also used in this study (8).

In their study performed on lab rats, Gomes et al. (31) applied xenograft to the socket after tooth extraction, then sacrificed the animals on the 1st, 7th, 14th, 21st, and 49th days, took radiography, and performed fractal analysis. In the grouping made according to duration,

they did not find any differences between the groups. However, it must be noted that waiting durations after the xenograft application were low and the time differences between the groups were also low in their study. When we check the mean fractal value, it was below 1, which is similar to our study. By using fractal analysis, Dursun et al. (17) compared the xenograft types in patients whom they treated with bilateral two-staged open sinus lift, and found no difference between the two groups. In their study, unlike ours, they took tissue samples from the relevant area six months after the first procedure, scanned these samples with micro ct, and conducted fractal analysis on the images. As a result, they found no difference between the two groups. Their fractal values after six months were above two, and these results are consistent with the results of neither our study nor similar studies (31-33).

CONCLUSION

In our study, we observed that the density of the xenograft material used in the open sinus lift tended to decrease starting from the period of three to six months after the surgery (**Figure**). We observed that nine months after the surgery, this density loss increased even more. This indicates that the initially dense areas within the graft resorb over time and are replaced by the trabecular bone. In conclusion, fractal dimension can be used as a method in the evaluation of ossification occurring after open sinus lift surgery

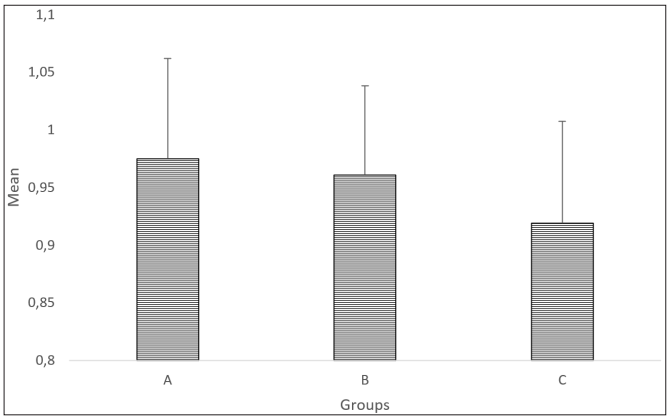

Figure. Mean and standard deviation graph according to groups

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for this study was granted by the Health Sciences Non-Invasive Clinical Researchs Ethics Committee of İnönü University (Date: 16-11-2021, Decision No: 2021/2686).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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The effect of the number of anchors used in the medial row on clinical outcomes in arthroscopic double row repair of rotator cuff tears: retrospective evaluation of patients with 3 to 7 years of follow-up

Bertan Cengiz

Acıbadem Kayseri Hospital, Department of Orthopaedics and Traumatology, Kayseri, Turkey

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ABSTRACT

Aim: Arthroscopic double row (DR) suture anchor repair is one of the most frequently applied methods in the surgical treatment of rotator cuff tear (RCT). Various modifications have been tried to eliminate some of the disadvantages of this technique such as operation time, high cost, and the high risk of retearing. In this study, we aimed to investigate whether placing a single or double suture anchor in the medial row affects clinical and functional outcomes and retear rates in patients with RCT who were operated with the DR suture anchor technique.

Material and Method: A retrospective study including 58 patients aged 18-65 years who underwent DR suture anchor repair due to medium-sized RCT and had a minimum follow-up period of 3 years was conducted. One knotless anchor was placed in the lateral row in all patients. In the medial row, we placed 1 all suture anchor (ASA) in group 1 and 2 ASAs in group 2. Visual pain scale (VAS), University of California Los Angeles Score (UCLA), American shoulder and elbow score (ASES) scales were used for preoperative and postoperative clinical and functional evaluation, and complications and retears were recorded.

Results: When the preoperative and postoperative VAS, UCLA and ASES scores were compared within groups, there were significant difference from pre- to post-operative findings in both groups ($p < 0.001$). However, there was no statistically significant difference between the groups in terms of preoperative and postoperative VAS, UCLA and ASES score ($p > 0.05$). Operation time in Group 1 was significantly shorter than in Group 2 ($p < 0.001$).

Conclusion: In DR suture anchor repair, there is no difference in clinical outcomes and retear rates in surgeries utilizing single or double suture anchor placement in the medial row. Increasing the number of anchors in the medial row does not contribute to clinical and functional results, and has disadvantages such as increasing operation time and cost.

Keywords: Rotator cuff tear, double row repair, retear, UCLA, ASES

INTRODUCTION

Rotator cuff tear (RCT) is the most common cause of shoulder pain in adults (1). Surgical treatment of RCTs, which can cause severe pain and weakness that limit daily activities and significantly hinder quality of life, has been applied for years, but procedural improvements are being made continuously (2,3).

Arthroscopic surgery has various advantages including reduced postoperative morbidity, pain and deltoid dysfunction, and therefore, is currently accepted as the gold standard treatment in rotator cuff repair (3). Among the various arthroscopic repair models, the most commonly used are single row (SR) and double row (DR) suture anchor techniques. The main difference of DR repair from SR repair is a second anchor series placed on the medial aspect of the tendon -in addition to the fact that anchors are placed on the lateral side of the tendon footprint (4). It was thought that with this technique, a wider restoration of the anatomical footprint could be achieved, the repair strength would be higher, less stress would occur on the anchors and knots, and better healing rates could be achieved (3). However, there is still no consensus on which technique achieves the best clinical and functional results (5-8). On the other hand, despite many advantages of arthroscopic repair, higher retear rates have been reported with these techniques (9,10). For this reason, studies are continuing on different modifications to increase clinical

Corresponding Author: Bertan Cengiz, drbertan@gmail.com
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efficiency, reduce complication rates, shorten operation time and increase cost effectiveness.

In this study, we aimed to investigate whether the number of sutures applied in the medial row had an effect on clinical outcomes and retearing rates in DR suture repair, which is one of the most commonly used techniques for RCT repair.

MATERIAL AND METHOD

In our retrospective study, the patient records of 329 patients who underwent arthroscopic RCT surgery in our hospital between 2014-2018 were evaluated. The study was carried out with the permission of the Acıbadem University Ethics Committee (Date: 14.10.2021, Decision No: 2021-20/44). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

The inclusion criteria were as follows: being aged 18-65 years, having medium sized RCT (1-3 cm) diagnosed by magnetic resonance imaging (MRI) according to the Deorio and Cofield classification, having undergone treatment with DR suture anchor repair, and attending follow-up studies for at least three years (11). Patients younger than 18 and those older than 65 years, those with a tear greater than 3 cm or less than 1 cm, those with a history of previous shoulder surgery, those who received steroid injections within the last 3 months, subjects who underwent SR cuff repair, patients who had DR cuff repair but had titanium suture anchor for the medial row or knotted suture anchor for the lateral row, those who had insufficient follow-up time, and individuals who had undergone revision surgery were excluded from the study.

Of the 329 patients examined, 58 patients who met these criteria were divided into 2 groups: Group 1 (n=31): 1 double-loaded four-strand all-suture anchor (ASA) for the medial row and 1 Peek anchor for the lateral row, and Group 2 (n=27): patients with 2 double-loaded four-strand all-suture anchors for the medial row and 1 Peek anchor for the lateral row.

Procedure

If the tear involved only the central supraspinatus region (anterior or posterior portions intact), or if it was U or V shaped, or if the retraction was less than 1 cm, we used only 1 medial anchor. If the tear involved the anterior or posterior of the supraspinatus, and therefore, the central tendon was displaced anteriorly or posteriorly by medial retraction (L-shape, reverse L-shape or Trapezoidal shape), or if the tear included the infraspinatus, or if there was a retraction of ≥1 cm (in short, if the patient had a more complicated and larger tear), 2 medial anchors were used. In patients, we used double-loaded four-strand ASA (2.9 mm; JuggerKnot®, Biomet Inc., Warsaw, IN, USA) for the medial row, while the knotless anchor was used for the lateral row (3.5 or 4.5 mm PushLock® anchor, Arthrex®, Naples, FL, USA).

In the clinical and functional evaluation of the patients, preoperative and postoperative (mean 56.9±12.9 months) visual analog scale (VAS), University of California at Los Angeles Score (UCLA), American Shoulder and Elbow Score (ASES) scales were used. In addition, complications and retears were recorded.

The VAS is the most widely utilized and easy to use pain rating scale (12). Pain is scored subjectively between a minimum of 0 (none) and a maximum of 10 (worst imaginable pain). The UCLA is a 35-point self-report scale assessing patients based on the pain, function, strength, movement and patient satisfaction subdimensions (13). The ASES is a 100-point self-report scale consisting of two sub-headings that evaluate pain and 10 different activities related to daily life (14).

Surgical Technique

The surgical procedure was performed under general anesthesia in the lateral decubitus position. All patients were operated by a single surgeon. Standard arthroscopic portals were opened; the posterolateral portal was used as the imaging portal, and the anterolateral and lateral portals were used as the working portal. First of all, other pathologies of the joint were detected by diagnostic arthroscopy. The biceps tendon was evaluated, and if there was a pathology of the tendon, necessary intervention was performed (tenodesis or tenotomy) according to the patient's age/size of the lesion/condition of the tendon. Acromioplasty was performed on each patient as a standard approach. After the tear was detected, the size of the tear was determined using a probe. The degenerate and fringing parts were debrided, followed by preparation of the footprint. During surgery, the medial row anchors were placed medially, closest to the chondral junction. A double-loaded four-strand ASA was used as the medial row anchor. According to the shape and size of the tear, the quality of the tendon and how much it could be mobilized, 1 or 2 ASAs were used. All threads of the anchor were threaded with the help of a suture threader, approximately 10 mm medial to the tear, leaving the appropriate distance between each suture. Then the medial row threads were knotted. If 1 ASA was used for the medial row, both knotted threads were loaded on the knotless anchor (PushLock) and placed 1-1.5 cm lateral to the greater tuberculum as lateral row anchors. If 2 ASAs were used, all threads were knotted in the medial row by passing through the rotator cuff, then all sutures were loaded onto the PushLock and placed as lateral row anchors.

Postoperative Rehabilitation

A shoulder abduction splint was used for 6 weeks in the postoperative period. Mild passive forward flexion exercises were started on the 2nd postoperative day. After 6-8 weeks, active assisted range of motion (ROM), active ROM and strengthening exercises were started gradually. Light activities were allowed after 3 months, and heavy activities and sports were allowed after 9 months.

Statistical Analysis

The SPSS version 18.0 Windows software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of obtained data. Categorical variables were compared using chi-squared tests. The Shapiro-Wilk test was used to determine normality of distribution. The comparison of quantitative differences between the groups was assessed with the Student's t-test or the Mann-Whitney test, depending on normality of distribution. The nonparametric Wilcoxon Signed Ranks test was used to test for differences between related (paired) samples. Differences with a p value of <0.05 were considered to be statistically significant.

RESULTS

Of the 329 examined patients, 58 were eligible for the study according to aforementioned criteria (**Figure**). The median (IQR) age of the patients was 58 (51-64) years; 26 were female and 32 were male. There was no significant difference between the two groups in terms of demographic characteristics, operated side and retear rates (p > 0.05). While the operation time was 62.19±6.25 minutes in Group 1, it was 72.22±4.98 minutes in Group 2. There was a significant difference between the two groups in terms of operation time (p < 0.001) (**Table 1**).

Table 1. Summary of patient characteristics with regard to groups

	Number of all-suture anchors			
	One (n=31)	Two (n=27)	All	
Sex				
Female	14 (45.2%)	12 (44.4%)	26 (44.8%)	0.956
Male	17 (54.8%)	15 (55.6%)	32 (55.2%)	
Age (year)	57 (50-62)	59 (53-64)	58 (51-64)	0.425
Side				
Left	15 (48.4%)	13 (48.1%)	28 (48.3%)	0.986
Right	16 (51.6%)	14 (51.9%)	30 (51.7%)	
Operation time (mins)	62.19±6.25	72.22±4.98	66.86±7.57	<0.001
Follow-up time (months)	55.68±13.3	58.22±12.56	56.86±12.91	0.459
Retear	3 (9.7%)	3 (11.1%)	6 (10.3%)	0.858

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution, and frequency (percentage) for categorical variables

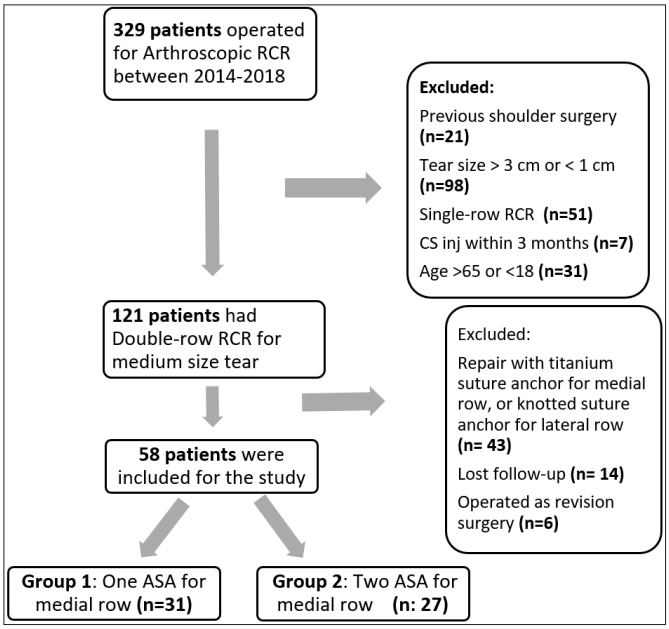

Figure. Flowchart of the study
RCR, Rotator cuff repair; CS, Corticosteroid; ASA, All-suture anchor.

A significant difference was found between the preoperative and postoperative ASES, UCLA and VAS scores of patients in both groups (p < 0.001). When group 1 and group 2 were compared in terms of preoperative and postoperative VAS, UCLA and ASES scores, no significant difference was found in any parameter (p > 0.05) (**Table 2**).

Table 2. Summary of the clinical outcomes with regard to the groups

	Number of all-suture anchors		p*
	One (n=31)	Two (n=27)	
ASES score			
Preoperative	40 (36-42)	42 (38-46)	0.280
Last follow-up	88 (86-92)	90 (88-92)	0.649
p**	<0.001	<0.001	
UCLA score			
Preoperative	14 (12-16)	14 (12-16)	0.349
Last follow-up	32 (28-32)	32 (30-34)	0.107
p**	<0.001	<0.001	
VAS score			
Preoperative	8 (7-8)	8 (7-8)	0.379
Last follow-up	3 (2-3)	2 (2-4)	0.579
p**	<0.001	<0.001	

ASES Score: American Shoulder and Elbow Score, UCLA: University of California at Los Angeles Score, VAS: Visual Analog Scale, Data are given as median (1st quartile-3rd quartile), *Between groups, **Within group

DISCUSSION

In our retrospective study, in which we compared two different modifications of the arthroscopic DR suture anchor rotator cuff repair technique, we did not find significant differences in clinical outcomes and complication rates in the two groups. However, the operation time was significantly shorter in recipients of a single suture anchor to the medial row.

Although there are conflicting results in studies comparing DR and SR repair methods, it is generally accepted that DR repair is more effective in large and massive tears (8,15-21). In their study comparing DR and SR repair in medium and large-sized tears, Koh et al. found no significant difference in clinical outcomes and complication rates between the two groups. Of note, one suture anchor was applied to the medial row in the patient group who underwent DR repair (17). Similarly, in our study, 1 suture anchor was applied to the medial row in Group 1, but unlike the mentioned study, the other group underwent repair via DR with 2 suture anchors, rather than SR. Nonetheless, our results also showed similar outcomes, but it must be noted that all patients in our study had a medium-sized tear according to the Deorio and Cofield classification.

Despite the successful results of suture anchor repair, there is still a risk of retear reported at varying rates (20-90%) in the literature (23). Although the risk of retear appears to be greater in SR suture anchor repair, retear risk is a general problem in arthroscopic rotator cuff repairs (24). Methods that can increase repair strength are necessary to reduce the risk of retearing (25). In some studies, the musculotendinous junction has been shown as the primary point of failure in patients who underwent DR repair (26). Revision of this region is difficult and the medial row should not be overstretched to avoid it (3). Medial insufficiency due to excessive load and tendon strangulation in the medial knots necessitates preventive measures to improve medial row integrity (3). In this study, we hypothesized that using changing the number of medial row sutures could be associated with medial row overstretching and medial insufficiency development. However, we did not find a significant difference between the two groups in terms of retear rates. The fact that our retear rates were low overall (10.3%) compared to the literature may be due to the small number of patients in the study and the inclusion of only medium-sized RCT cases.

Depending on the suture anchor repair, there are other problems such as dislodgement of the anchor, impingement of the knot, difficulty in revision and high costs (27). In order to overcome these problems, studies are carried out on different techniques which employ various approaches, including reducing the number of anchors, repairing without anchors, reducing the number of sutures, or changing the configuration (27-30). The DR technique also has other disadvantages, such as prolonged operation time, steep learning curve, and the fact that it is a relatively complicated and expensive procedure (8,15-18). Various studies have been carried out on different modifications of the DR technique in order to shorten operation time, simplify the procedure (albeit partially), and to reduce complication rates. In a recent review, out of 9 studies comparing different DR configurations, none showed a significant superiority over the others in terms of clinical outcomes (22), indicating that these modifications have had little effect on outcomes. It is known that increased duration of surgical operations is associated with increased risk of infection, transfusion likelihood and thrombosis development (31). As mentioned above, since there no significant differences have been reported between clinical and functional results in different arthroscopic rotator cuff surgery models, complications and costs gain importance in addition to various factors determining the choice of surgical approach. In our study, operation times were significantly lower in single anchor recipients. In this respect, our study results can be seen as preliminary data for more detailed studies aimed at reducing the costs and possible complications related to prolonged operation times.

It has been suggested that increased operative time may also have an effect on the retear rates, and various studies have been conducted to seek possible relationships. Le et al. found that longer operative time was correlated with increased retear rate (32). In another study, authors found that the duration of surgery did not have a significant independent effect on rotator cuff retear rates at the postoperative 6th month (31). In our study, while there was a significant difference between the two groups in terms of operation time, there was no significant difference between the retear rates.

Our study has some limitations such as its retrospective design and the relatively low number of patients. The fact that the study was single-centered and only included non-severe tears also limit generalizability. In addition, since the decision for surgical approach (exposure) was based on a pre-defined protocol according to patient- and tear-based characteristics, outcomes could have been influenced by differences in management approaches and post-operative care throughout the study period. Therefore, larger-scale multicenter prospective studies would be more beneficial to investigate the advantages and disadvantages of these different modifications.

CONCLUSION

In DR suture anchor repair of rotator cuff tears, increasing the number of anchors in the medial row does not contribute to clinical and functional results; in fact, this approach has disadvantages such as increasing operation time and costs. There is a need for prospective studies with a larger number of patients with better categorization.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Acıbadem University Ethics Committee (Date: 14.10.2021, Decision No: 2021-20/44).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Pain levels of patients undergoing ultrasound guided biopsies and associated factors: a cross-sectional study

Mustafa Emre Akın

Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Department of Radiology, Ankara, Turkey

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ABSTRACT

Aim: Patients may experience pain in minimally invasive biopsy procedures. It is important to evaluate the degree of pain and to know the factors that determine the level of pain felt by patients for adequate pain management. The aim of this study is to determine the pain levels felt by patients and socio-demographic and clinical factors associated with higher pain levels in breast and liver biopsy procedures.

Material and Method: In this cross-sectional observational study, patients who will undergo ultrasound-guided breast and liver biopsy procedures in the study center were invited to the study. The pain level was measured with the Visual Analogue Scale (VAS). Pain measurements above 45mm were classified as moderate-to-high pain levels. The State-Trait Anxiety Scale was used to measure the anxiety levels of the patients and the radiologist. Sociodemographical (sex, age, education level, job, income) and clinical factors (biopsy site, duration, bosy mass index, anxiety level of the patient and the radiologist) that may be associated with the pain levels of the patients were analyzed.

Results: The sample consisted of 76 patients, 62 were female (81.6%). The procedures consisted of 43 breast biopsies (56.6%), 33 liver biopsies (43.4%). The median pain level measurement determined by the VAS is 20.0mm (IQR: 9.3- 38.5). Most of the sample (59.2%) stated that they felt mild pain. It was found that patients with higher anxiety levels and patients underwent liver biopsy had statistically significantly higher moderate-to-high pain levels than patients with lower anxiety (OR: 3.683 95% CI: 1.159- 11.705, p=0.220), patients who underwent breast biopsies (OR: 3.521, 95% CI: 1.153- 10.752, p=0.023). A positive correlation was found between the level of pain and the level of anxiety (r=0.267, p=0.020).

Conclusion: This study demonstrated that most ultrasound-guided biopsy procedures were performed with mild or no pain although higher patient anxiety levels were associated with higher pain levels during the procedures. Patients undergoing liver biopsy procedures had higher pain levels than breast biopsy procedures.

Keywords: Ultrasonography, biopsy, pain, breast, liver

INTRODUCTION

Minimally invasive biopsy procedures performed with radiological imaging are safe and provides comfort for patients with few side effects and short hospital stays. Therefore, ultrasound guided percutaneous breast and liver biopsies are preferred over open surgery and frequently performed (1-4). Nevertheless, it is known that patients experience distress and pain even in these minimally invasive radiological procedures (5).

Reducing the pain that the patients feel during minimally invasive biopsy procedures is important for many reasons. Firstly, it increases the patient's comfort. Additionally, pain and the fear of pain can be a reason for patients to delay the biopsy procedure. Patients who feel more pain during the procedure have been reported to have difficulties in compliance with follow-up and treatment (5), even hospitalization may be required due to the pain felt after biopsy procedures (6). For adequate pain management it is important to evaluate the degree of pain and to know the factors that affect the level of pain felt by patients during minimally invasive biopsy procedures.

It has been reported that patients who underwent ultrasound guided breast and liver biopsies feel some degree of pain (7-9). Pain sensation may be affected by many factors. The most important associates of pain during ultrasound guided liver and breast biopsy procedures in the literature were anxiety (7,10) and female sex (11). As all of the studies in the literature included only one biopsy site, there is a gap in the literature in comparison of pain

Corresponding Author: Mustafa Emre Akın, dremreakin@gmail.com
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levels between breast and liver biopsy sites and studies aiming to report both clinical and socio-demographical associates of pain during biopsy procedures.

While it is necessary to know the pain levels and associated factors for breast and liver biopsy procedures, two most common minimally invasive biopsy procedures; the aim of this study is to determine the pain levels felt by patients and socio-demographic and clinical factors associated with higher pain levels in breast and liver biopsy procedures. It has been hypothesized that patients who undergo liver biopsy procedures would experience higher levels of pain than patients who undergo breast biopsy and also anxiety level of patients and the physician was associated with higher pain levels.

MATERIAL AND METHOD

All of the procedures followed were in accordance with the Helsinki Declaration. Ethical approval was obtained from the Institutional Review Board of Yıldırım Beyazıt University Yenimahalle Trainig and Research Hospital for this study (Date: 13.10.2021, Decision No: E-2021-55).

The research was carried out in a cross-sectional and observational design. Patients who will undergo ultrasound guided breast and liver biopsies in the radiology department of the Yıldırım Beyazıt University Yenimahalle Trainnig and Research Hospital between October 15, 2021 and December 1, 2020 were invited to the study. Inclusion criteria were determined as being able to speak Turkish, being able to read and write, being over the 18 years of age. All patients were asked to sign written consent to participate in the study. Those with a previously diagnosed anxiety disorder or other psychiatric diseases, and those with a history of regular anxiolytic and analgesic use were excluded from the study.

All ultrasound guided biopsies performed in the Radiology Department of the study center are performed by the researcher radiologist. The patients who met the inclusion criteria and underwent ultrasound guided biopsy procedures were invited to the study during their appointments. Written consent and socio-demographic information forms were obtained from patients before starting the biopsy procedure. Socio-demographic form included information on patients' sex, age, education level, job and income to find out whether these factors were associated with pain.

All biopsy procedures were performed by the researcher, an experienced radiologist using aseptic technique and local anesthesia. Breast biopsy patients underwent ultrasound examination of the biopsy site with Toshiba Aplio 500 ultrasound machine (Toshiba Medical Systems, Otawara-Shi, Japan) using a 14MHz ultrasound probe. For local anesthesia, 2 ml of 2% prilocaine without epinephrine was administered superficially followed by 10 ml of 2% prilocaine without epinephrine around the lesion. After performing 2 mm length skin incision, under ultrasonographic guidance, 16G biopsy needle was used to obtain biopsy material. Liver biopsy patients, after lateral decubitus positioning, underwent ultrasound examination with Toshiba Aplio 500 ultrasound machine (Toshiba Medical Systems, Otawara-Shi, Japan) using a 3.5MHz ultrasound probe. After superficial injection of 2 ml of 2% prilocaine without epinephrine, 10 ml of 2% prilocaine without epinephrine was administered to the deep soft tissues and around liver capsule. Following performing 2 mm length skin incision, through appropriate intercostal space, 16G biopsy needle was used to obtain biopsy material under ultrasonographic guidance. All liver biopsies were performed for parenchymal sampling.

After the wound dressing has ended, the participants were given pain and anxiety measures to fill. In addition, the researcher physician filled out the anxiety measure after each biopsy procedure and stated his momentary anxiety levels during that procedure. Biopsy duration was recorded by the researcher.

The Visual Analogue Scale (VAS) was used to measure the pain felt by the patient during biopsy. This scale is widely used to measure and follow-up pain levels in many studies over years (12,13). This scale consists of a 100 mm horizontal line ruler with the feeling no pain at one end and unbearable pain at the other representing the minimum and maximum scores for pain. The ends of the scale were marked 'no pain' and 'most severe pain'. There were no intermediary markings on the scale. In this study, values between 0-4mm were classified as "no pain", values between 5-44mm as "mild pain", values between 45-74mm as "moderate pain" and values between 75-100mm as "severe pain" (11-14). The patients were asked to draw a vertical line representing their pain levels. The value was measured and recorded in milimeters by the researcher.

The State-Trait Anxiety Scale (STAI) was used to measure the anxiety levels of the patients and the radiologist. This scale was developed by Spielberger et al. in 1970, and is a Likert-type scale (four degrees varying from "none" to "completely") that measures state and trait anxiety levels with 20 questions separately (15). It consists of two subscales with 20 items each. The State Anxiety Scale aims to measure how the patient feels at the moment whereas the Trait Anxiety Scale aims to measure how the patient feels in general daily life as a self-report. The

total score obtained from both scales varies between 20 and 80. Higher scores indicate high anxiety levels while lower scores indicate low anxiety levels (15). Validity and reliability study of the scale in Turkey was performed (16). The measure that has been frequently used in previous studies on radiological biopsy procedures (17-20). In the study, both the patients state anxiety scores reflecting their anxiety levels during the biopsy procedure and their trait anxiety scores reflecting their general anxiety levels were investigated as associates of pain during the biopsy procedures. Additionally, if the state or trait anxiety levels of the patients were found to be high, the patient was consulted to psychiatry.

Numerical variables were expressed as mean and standard deviation (SD) if distributed normally; median and interquartile range (IQR= 25%-75%) values if not. The Shapiro-Wilk test was used to determine the distribution of data. Categorical variables were given as numbers and percentages. The differences of pain levels between two groups were tested with Student-t test if distributed normally, with Mann Whitney-U test if not. Pearson correlation analysis was used for investigating the relationship between pain and anxiety scores. To find the association between feeling moderate-to-severe pain during procedures with patients' clinical and socio-demographical variables Pearson Chi-Square test and Fisher Exact tests were used. The results were considered statistically significant when $p < 0.05$ and 95% confidence interval (CI). Statistical analyses were done using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program.

RESULTS

Out of 81 patients who underwent ultrasonography-guided biopsy during the study period; 3 patients with a previously diagnosed anxiety disorder and 2 patients with a history of regular analgesic use were excluded. Remaining 76 patients who provided informed consent comprised the sample of the study.

Sixty-two participants were female (81.6%), 14 were male (18.4%). The mean age of the participants was 43.2±11.4 (**Table 1**). The youngest patient was 19 years old, and the oldest patient was 75 years old. Breast biopsy was performed for 43 patients (56.6%), and liver biopsy was performed for 33 patients (43.4%). Most of the sample had education less than 12 years (78.9%) is and participants who had a job to sustain regular income constitute 30.3% of the sample. The mean biopsy time was 15.9±3.7 minutes overall which was 17.3±3.8 minutes in breast biopsies and 14.0±2.5 minutes in liver biopsies, and the difference was statistically significant (p=0.047).

Table 1. Sociodemographic characteristics of the sample

Sociodemographic characteristics (N=76)	
Age (mean±SD*)	43.2±11.4
Sex (n, %)	
Female	62 (81.6)
Male	14 (18.4)
Occupation (n, %)	
Housewife	42 (55.3)
Working	23 (30.3)
Unemployed	4 (5.3)
Retired	7 (9.2)
Educational background (n, %)	
Primary school	25 (32.9)
Middle school	18 (23.7)
High school	17 (22.4)
University graduate	16 (21.1)

*SD: Standard deviation

The median pain level measurement of the sample determined by the Visual Analogue Scale is 20.0mm (25% -75%: 9.3-38.5). According to the VAS results, 14 patients (18.4%) stated that they did not feel any pain, 45 patients (59.2%) felt mild pain, 14 patients (18.4%) felt moderate pain, and 2 patients (2.6%) stated that they felt severe pain. The median pain level of the patients who underwent breast biopsy was 13.0mm (IQR: 4-23); the median pain score of the patients who underwent liver biopsy was 28mm (IQR: 18-49) and the difference was statistically significant (p=0.001)

The mean state anxiety level of the sample was 44.0±5.9; trait anxiety level was 50.1±6.8; the mean state anxiety level of the researcher who performed the biopsy procedure was 44.2±2.0. The mean state anxiety level of researcher was 44.6±2.0 in the breast biopsies which was higher than 43.6±1.7 in the liver biopsies (p=0.020).

The relationships between the patient's feelings of moderate-to-high pain and the patient's socio-demographic and clinical characteristics were examined (**Table 2**). In these bivariate analyses, patients who reported higher anxiety levels felt significantly more pain than patients reported lower anxiety levels [Odd's ratio (OR): 3.683 95% CI: 1.159-11.705, p=0.220] and it was determined that the patients who underwent liver biopsy felt significantly more moderate-to-high levels of pain than those who had underwent breast biopsy (OR: 3.521, 95% CI: 1.153-10.752, p=0.023). A statistically significant positive correlation was found between the level of pain felt by the patient during biopsy and the level of anxiety (r=0.267, p=0.020).

Table 2. Bivariate analysis between the moderate-to-high level of pain levels and their sociodemographic and clinical characteristics

Sociodemographic characteristics		Rates		Feeling moderate-to-high level of pain				
		n	%	n	%	OR	95 % CI*	p
Sex	Female	62	81.6	16	25,0	1.667	0.330-8.423	0.720
	Male	14	18.4	2	16,7			
Age	>50	22	28.9	7	31,8	1.824	0.598-5.564	0.287
	≤49	54	71.1	11	20,4			
Education	>12 years	16	21.1	3	18,8	0.692	0.173-2.765	0.748
	≤12 years	60	78.9	15	25,0			
Regular income	Present	30	39.5	10	33,3	2.375	0.810-6.965	0.110
	Absent	46	60.5	8	17,4			
Clinical characteristics								
Biopsy site	Liver	33	43.4	12	36.4	3.521	1.153-10.752	0.023
	Breast	43	56.6	6	14.0			
Biopsy duration	≤15 minutes	40	52.6	12	30.0	2.141	0.708-6.493	0.172
	>15 minutes	36	47.4	6	16.7			
BMI**	>30	15	19.7	6	40.0	2.722	0.811-9.135	0.171
	≤30	61	80.3	12	19.7			
State anxiety scale score of the patients	>46	37	48.7	13	35.1	3.683	1.159-11.705	0.220
	≤45	39	51.3	5	12.8			
Trait anxiety scale score of the patients	>46	55	72.4	14	25.5	1.451	0.417-5.049	0.764
	≤45	21	27.6	4	19.0			
State anxiety scale score of the radiologist	>46	15	19.7	2	13.6	0.433	0.880-2.131	0.499
	≤45	61	80.3	16	26.2			

*CI: Confidence interval, **BMI: Body mass index

DISCUSSION

In minimally invasive imaging-guided biopsy procedures, it is important to reduce the pain of patients and increase their comfort. In this study patients mostly felt minimal pain during ultrasound guided breast and liver biopsy procedures. The findings of the study showed that patients who underwent liver biopsy experienced a statistically significantly higher level of pain than those who underwent breast biopsy, and also that patients who were more anxious during biopsy felt higher levels of pain.

In this study, approximately 75% of the sample who underwent ultrasound guided biopsy stated that they did not feel any pain or felt mild pain. The median pain level of patients who underwent breast biopsy was 13.0mm (IQR: 4-23), and it is consistent with the mild pain levels found in the breast biopsy study conducted by Soo et al. (7) on 136 women from the United States. The median pain level of the patients who underwent liver biopsy was 28mm (IQR: 18-49). According to the literature, it was reported that patients felt moderate and severe pain in liver biopsies (8,9,20). Low levels of pain reported in this study can be explained by the experience of the center, the application of local anesthesia during the procedure or the fact that the physician performing the biopsy was a researcher which may lead to patients' inclination to report lower pain levels.

In previous studies, the pain felt in ultrasound guided biopsies was found to be related to the age of the patient, low education level, being a woman, anxiety level, the number of biopsy procedures, physician-patient relationship, the experience of the person performing the biopsy, and the characteristics of the biopsy needle (7-9, 20-22). The reason for not finding a relationship between female gender and pain level in this study may be that all breast biopsies, which make up approximately half of the sample, were applied to women and breast biopsies were less painful or painless. In this study although the procedure duration of breast biopsies was found to be longer than liver biopsies and patients reported more anxiety in breast biopsies, it is shown that the pain levels felt by patients in liver biopsies were higher than pain levels reported in breast biopsies. In liver biopsies, passing through the peritoneum and liver capsule as well as skin, subcutaneous tissue, muscle tissue may explain the higher level of pain compared to breast biopsies (23). Another important finding is that patients who have higher anxiety levels during biopsy procedures experience higher levels of pain. This finding is compatible with many studies in the literature (7,20,21). The absence of a significant relationship between body mass index and pain in this study is consistent with the literature (7). In addition, the relationship between the physician's spontaneous anxiety level during biopsy and the pain felt by the patient was investigated for the first time in this study, but a significant relationship was not found.

The findings of this study may help to guide clinical studies. It is important to reduce the parient's anxiety in ultrasound guided biopy procedures. It may be helpful to inform the patient before the biopsy and conduct an interview to reduce anxiety. The clinicians must consider recommending relaxation techniques and anxiolytics

for reducing and managing anxiety levels of patients (24-26). Especially in patients undergoing liver biopsy, it is important to use effective analgesics in addition to reduce anxiety.

The study has some important limitations. The first is that the cross-sectional pattern limits cause and effect relationships between pain and anxiety. Conducting the study with a sample with low socioeconomic level and not including other biopsy sites other than breast and liver prevents the generalization of the findings to all ultrasound guided biopsy procedures. It should be noted that the pain levels during the biopsy procedures may be affected by many intrinsic and extrinsic factors which may not be controlled in this study. In addition, since the physician performing the biopsy procedure was also the researcher, there may be bias in patients' self-reports of their pain and anxiety levels.

CONCLUSION

Despite these limitations, there are strengths of this study. When investigating factors associated with pain which is a subjective feeling and is affected by many conditions; this study has taken comprehensive factors into consideration such as gender, education level, income level, many clinical characteristics and the physician's anxiety level during the biopsy procedure for the first time. In conclusion, the findings of this study show that most ultrasound guided biopsy procedures were performed painless or with mild pain, and that the biopsy site and the patient's anxiety levels were associated with the pain during the procedure. Using techniques that will reduce anxiety and use of effective analgesia even in minimally invasive biopsy procedures are important for pain management and patient comfort.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Institutional Review Board of Yıldırım Beyazıt University Yenimahalle Trainig and Research Hospital for this study (Date: 13.10.2021, Decision No: E-2021-55).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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