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EDITORIAL

Dear Readers,

We are proud to publish the our journal's 3th issue of 2023 with highly scientific new articles. Currently, 6 years has been passed since our journal's establishment and we are trying to raise our scientific bar day by day. As we have mentioned before, we are increasingly contributing to the international literature step by step. We are constantly working to raise our scientific bar and to increase the success of our journal by entering valuable international indexes . We would like to thank all the authors who contributed to the strengthening of our journal by sending articles from both domestic and abroad.

Sincerely Yours,

Assoc. Prof. Alpaslan TANOGLU, MD, PhD
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Evaluation of abdominal vascular structures by multidetector computed tomography in Crimean–Congo hemorrhagic fever patients

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ABSTRACT

Aim: This study aims to determine whether Crimean–Congo Hemorrhagic Fever (CCHF) has effects on abdominal vascular structures.

Material and Method: The study group included 35 patients diagnosed with CCHF. The control group included 35 patients with symptoms such as dyspepsia, pelvic pain, and abdominal pain who underwent multidetector computed tomography (MDCT) and whose MDCT examinations were reported as completely normal. This is a retrospective study and patients admitted to the hospital between May 2016 and April 2022 were included in the study. The patient group and control group were compared in terms of liver size, splenic size, and portal vein (PV), hepatic artery (HA), splenic vein (SV), splenic artery (SA), superior mesenteric vein (SMV) and superior mesenteric artery (SMA) diameters.

Results: The liver size, splenic size, and PV, HA, and SA diameters in the patient group were significantly higher than those in the control group ($p<0.001$). While the SV, SMV, and SMA diameters were higher in the patient group than in the control group, the differences were not significant ($p>0.05$).

Conclusion: Our study shows that abdominal vascular structures are affected in CCHF patients.

Keywords: Crimean–Congo hemorrhagic fever, multidetector computed tomography, portal vein, superior mesenteric vein

INTRODUCTION

Crimean–Congo hemorrhagic fever (CCHF) is a viral zoonotic disease that is characterized by hemorrhage and fever and can be fatal (1-4). It is transmitted to humans through contact with infected secretions and blood of humans or animals or through tick bites (5-7). The pathogenesis of the disease is not completely known. However, it is known to affect some target cells, including endothelial cells and hepatocytes. In particular, endothelial cells are severely affected by the disease (8). Although the destruction of the vascular endothelium by the virus is known, there are insufficient studies in the literature on changes in abdominal vascular structures that may develop due to the disease (9-11). Therefore, our study aims to assess whether any diameter changes are detected on abdominal multidetector computed tomography (MDCT) in CCHF in the portal vein (PV), hepatic artery (HA), splenic vein (SV), splenic artery (SA), superior mesenteric vein (SMV), and superior mesenteric artery (SMA). We think that our study may pave the way for more comprehensive studies on abdominal vascular structures in CCHF.

MATERIAL AND METHOD

Our study was planned retrospectively. The study was carried out with the permission of University Hospital, Noninvasive Clinical Ethics Committee (Date:28.02.2022 Decision No:22-KAEK-140). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Our study consists of 35 patients who were admitted to our hospital between May 2016 and April 2022 and were diagnosed with CCHF, and 35 individuals constituting the control group who underwent MDCT with symptoms such as dyspepsia, pelvic pain, and abdominal pain and whose MDCT examinations were reported as completely normal.

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Patients with malignancy, acute or chronic heart or lung failure, blood disease, chronic liver disease, or inflammatory bowel disease in addition to CCHF disease, patients with benign or malignant lesions of the spleen and liver, patients with any chronic gastrointestinal disease, and those who had undergone abdominal surgery or radiotherapy were not included in the patient group. Patients' medical information was obtained from their files.

The control group consisted of patients with nonspecific symptoms such as dyspepsia, pelvic pain, and abdominal pain who underwent abdominal MDCT examination and for whom no radiological findings were detected as a result of the examination. The control group was demographically similar to the patient group and consisted of patients without any additional disease.

MDCT Protocol

The MDCT protocol was applied by using 128-channel MDCT (GE Healthcare, Milwaukee, WI, USA). Consecutive axial sections of 5 mm slice thickness were obtained by abdominal MDCT. Automatic tube modulation at 120– 220 mA. The patient was in the supine position during the examination.The patients were asked to hold their breath during the examination.

Evaluation of MDCT Images

All images were evaluated by a radiologist who had at least 5 years of experience in abdominal radiology. For all patients in the study group, liver and spleen sizes were measured from the mid-clavicular line by creating coronal reformatted images (10). A liver size above 16 cm was defined as hepatomegaly. Spleen size above 12 cm was defined as splenomegaly (10). A gallbladder wall thickness greater than 3 mm was considered as gallbladder wall thickening (10). Measurements of vascular structures were made by taking the largest diameter of the vessel in the axial section of the abdominal window in MDCT of the abdomen. Portal vein and HA diameters were measured at the level of the liver hilum, and SV and SA diameters were measured at the level of the splenic hilum in the axial plane (**Figure**). The diameter of the superior mesenteric vein was measured in the axial plane from the first 2 cm after the origin of the portosplenic junction, and the SMA diameter was measured from the first 2 cm after the origin of the SMA from the aorta in the axial plane (12). The study group was compared with the control group.

Statistical Analysis

The statistical significance level of p was 0.05. Statistical analysis was performed using commercial software (SPSS 22.0 Chicago, IL, USA). On qualitative variables Chi-square test was used for comparison.

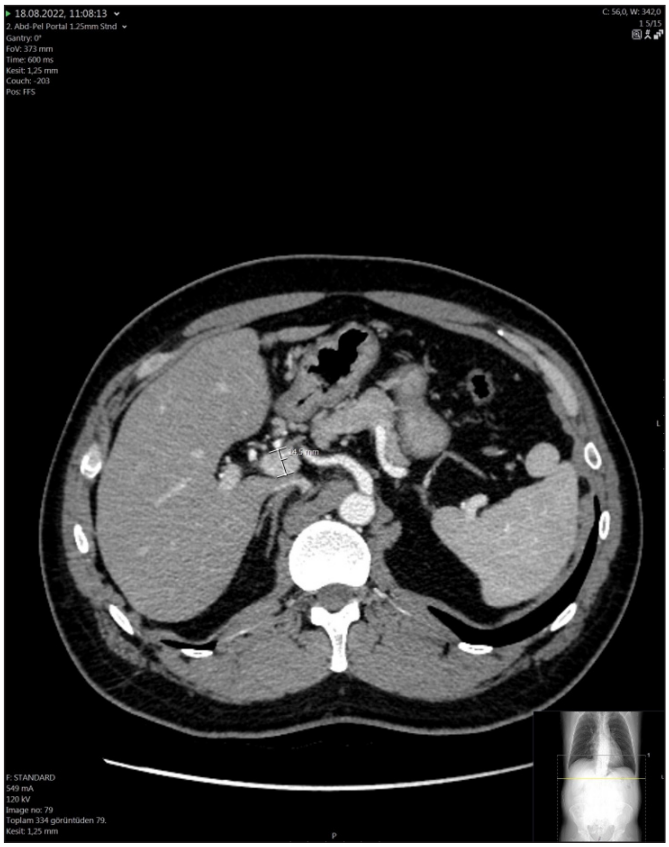

Figure. Measurement of portal vein diameter at the level of the liver hilum in axial multidetector computed tomography

RESULTS

Our study group consisted of 35 CCHF patients (20 males and 15 females) and 35 control patients (18 males and 17 females). The mean age of the CCHF patient group was 57, and the mean age of the control group was 52.63. There were no statistically significant differences between the patients and controls in terms of age and sex (p>0.05) (**Table 1**).

Table 1. Age and gender distribution of the control and patient groups

	Groups		p
	Control	Patient	
	Mean±SD	Mean±SD	
Age	52.63±20.17	57±14.7	0.299
Gender	1.48±0.50	1.41±0.50	0.565

In the evaluation of MDCT examinations of the patients, we found hepatomegaly in 22 (62.8%) patients, pleural effusion in 11 (31.4%) patients, abdominal free fluid in 7 (20%) patients, splenomegaly in 6 (17.1%) patients, mesenteric and omental adipose tissue heterogeneity in 4 (11.4%) patients, gallbladder wall thickening in 3 (8.5%) patients, parenchymal consolidation in 3 (8.5%) patients, pericardial effusion in 2 (5.7%) patients, and a decrease in periportal density detected in the form of a sheath representing periportal edema in 2 (5.7%) patients (**Table 2**).

Table 2. MDCT findings of the 35 patients with CCHF

Findings	Number of patients (n)	%
Hepatomegaly	22	62.8
Pleural effusion	11	31.4
Splenomegaly	6	17.1
Abdominal free fluid	7	20
Mesenteric and omental heterogeneity	4	11.4
Gallbladder wall thickening	3	8.5
Parenchymal consolidation	3	8.5
Pericardial effusion	2	5.7
Decrease in periportal density	2	5.7

The patient group and the control group were compared in terms of liver size, splenic size, and PV, HA, SV, SA, SMV, and SMA diameters. The liver size, splenic size, PV, HA, and SA diameters in the patient group were significantly larger than those in the control group ($p<0.001$). SV, SMV, and SMA diameters were larger in the patient group than in the control group, but no statistically significant differences were found ($p>0.05$) (**Table 3**).

Table 3. Liver size, splenic size, portal vein, hepatic artery, splenic vein, splenic artery, superior mesenteric vein and superior mesenteric artery diameters in the control and patient groups

	Groups		p
	Control	Patient	
	Mean±SD	Mean±SD	
Liver size	16.08±1.40	17.36±1.76	0.001
Splenic size	8.93±1.61	10.36±1.96	0.001
PV	12.53±1.3	13.61±2.04	0.010
HA	4.2±0.63	4.86±0.98	0.001
SV	7.93±1.52	7.99±1.57	0.852
SA	4.21±0.77	5.83±1.1	0.001
SMV	10±1.46	10.75±1.9	0.066
SMA	7.01±1.13	7.46±1.69	0.200

DISCUSSION

Crimean-Congo Hemorrhagic Fever begins with the virus entering the body through mucous membranes, or by inhalation. The virus can have direct toxic effects on the liver, spleen, and endothelial cells. This toxic effect stimulates the release of cytokines and chemokines from defense cells and may lead to an intense inflammatory response as well as endothelial damage. Considering the pathophysiological mechanisms at the molecular level, this process, which is caused by many inflammatory factors, is associated with increased endothelial damage and vascular permeability. Due to this toxic effect of the disease on endothelial cells, some studies have been conducted on changes caused by the disease in vascular structures (7,13-18). Two previous studies evaluated Doppler findings in the carotid and vertebral arteries in CCHF disease (19,20). Karavas et al. (19) and Salk et al. (20) found that peak end systolic and diastolic flow rates of bilateral carotid arteries and vertebral arteries were elevated in CCHF patients. These studies have shown that there are alterations in the vascular system in CCHF patients.

Aktas et al. (7) found a significant increase in the diameter of both main pulmonary arteries and pulmonary trunks in CCHF patients in their study on the thoracic findings in the disease. Karavas et al. (19) conducted a study on the abdominal findings of the disease with Doppler US. In their study, they found a significant increase in portal vein flow velocity in CCHF patients. They also found that liver size, spleen volume, and portal vein and splenic vein diameters were significantly larger in CCHF patients. In our study using MDCT, we evaluated liver size, spleen size, and PV, HA, SV, SA, SMV, and SMA diameters in CCHF patients. In our study, we found that liver and spleen sizes were significantly larger in the patient group compared to the control group ($p<0.01$). There was also a significant increase in PV, SA, and HA diameters in the patient group compared to the control group ($p<0.01$). Although SV, SMV, and SMA diameters were larger in the patient group compared to the control group, these differences were not statistically significant. The results of our study are compatible with the literature. A significant increase in diameter is observed in CCHF patients in the majority of abdominal vascular structures. These vascular structures especially concern the liver and spleen. In our previous studies (10,11), the most common findings in CCHF disease were hepatomegaly and splenomegaly. The increase in diameter, especially in PV, HA, and SA, in our study may be the cause of hepatomegaly and splenomegaly. The involvement of these vascular structures is thought to be due to the intense inflammatory response and endothelial damage caused by the pathophysiological mechanisms we mentioned before. The absence of a significant increase in SMV and SMA diameters in our study may explain that the changes seen in mesenteric and omental fatty tissue and intestinal loops are relatively less than the changes seen in liver and spleen in CCHF patients. Although the structures affected by the disease in the abdomen and the resulting findings are quite different, it is thought that the common point of all findings is endothelial damage and systemic inflammation.

The Most Important Limitations of Our Study

The study was conducted retrospectively on MDCT data. Therefore, only diameters of vascular structures were evaluated, but no comment can be made on vascular flow. Our study was conducted with a small group of patients. The reason for this is that while CCHF disease is endemic, the disease shows mostly thoracic findings, and abdominal MDCT is deemed necessary only in a small group of patients.

CONCLUSION

Our study shows that abdominal vascular structures are affected by the disease in CCHF patients. It is thought that these changes in the vascular structures may be responsible for the complications seen in the abdomen.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University Hospital, Noninvasive Clinical Ethics Committee (Date:28.02.2022 Decision No:22-KAEK-140).

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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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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Outcomes of multiple pregnancies: results of a perinatology clinic in a tertiary health center

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ABSTRACT

Aim: To evaluate maternal-fetal risks and pregnancy outcomes in multiple pregnancies.

Material and Method: The study included 226 patients with multiple pregnancies who applied to the Perinatology clinic of Izmir Tepecik Training and Research Hospital between January/2020 and December/2022. The data of the patients were recorded and evaluated retrospectively using the hospital database.

Results: Of 226 patients, 211 were twins, 14 were triplets and one was quadruplet. Pregnancy occurred after in vitro fertilization (IVF) in 116 patients and after donation in 1 patient. 55.7% of the patients were older than 35 years. While 137 pregnants (60.6%) were primiparous, 89 patients (39.3%) had a previous pregnancy. While 20 of the twin pregnancies delivered before the 25th gestational week, this number was found to be 7 for triplets. 202 (89.3%) of all multiple pregnant women were delivered by cesarean section. Hypertensive disorder was found in 28 of the twin pregnancies and in 4 of the triplet pregnancies. Gestational diabetes was observed in 41 twin and 3 triplet pregnancies. Small for gestational age (SGA) was observed in 121 twins, 13 triplets and 1 quadruplet pregnancy. Intrauterine growth retardation (IUGR) was observed in 76 twins and 6 triplets. The number of multiple pregnancies with a birth weight less than 2500 g was found to 187 (82.7%) in total. Major congenital anomalies of various organs (cardiac, central nervous system, etc.) were observed in 8 (3.5%) pregnant women.

Conclusion: Preterm birth, increased maternal morbidity and increased cesarean section frequency are some of the risks of multiple pregnancies. These risks can be reduced by knowing the potential risks of multiple pregnancies and by more careful follow-up starting from the early stages of pregnancy.

Keywords: Pregnancy, multiple, pregnancy complications, premature birth, pregnancy outcome

INTRODUCTION

Multiple pregnancy rates vary in different parts of the world. While it is less than 1% of all births in South Asia, this rate is more than 3% in the United States and France (1-3). However, this rate is increasing in developed countries which was 2% in the United States in the 1980s and 3.3% in 2009 (4). Postponing 'the desire to conceive' to older ages and using assisted reproductive techniques more frequently, seems to be the main reasons for the increase in the number of multiple pregnancies (5). The data for Turkey are similar (2.9% of all births in 2020 were multiple births. 96.8% of these births were twins, 3.1% were triplets and 0.1% were quadruplets) (6). While the twin birth rate was 2.8% in 2012, it increased slightly to 2.9% in 2020.

Multiple pregnancies can lead to an increase in perinatal morbidity (7). This increase is mostly due to the increase in the frequency of preterm birth. Especially in low and middle-income countries, early neonatal mortality due to preterm birth is 7 times more common (7). Low birth weight and intrauterine growth retardation (IUGR) are also common conditions. In addition, the morbidity of the second twin is higher in twins compared to the first twin (8). The negative effect of multiple pregnancies is not only on the fetus. At the same time, there are also maternal negative effects (9). It has been found that 'near miss' cases are more common in women with multiple pregnancies, especially in low and middle-income countries (9). The incidence of postpartum hemorrhage and hypertensive disorders is 4 times higher.

In this study, we evaluated the prognosis, complications and pregnancy outcomes of multiple pregnancies. We tried to find whether there is an increased risk in multiple pregnancies and, if so, at what rates these risks increase.

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MATERIAL AND METHOD

This study was approved by the Izmir Tepecik Training and Research Hospital Ethics Committee (Date: 2023, Decision no: 2023/02-39). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who applied to Izmir Tepecik Training and Research Hospital Perinatology Clinic between January/2020 and December/2022 were included in the study. The information of all patients with multiple pregnancies was documented using the hospital database and archive. The patients' ages, number of pregnancies, weeks of gestation, laboratory values, chorionicity, conditions during pregnancy follow-up and pregnancy results were scanned from the archive. Patients whose information could not be reached from the hospital database were not included in the study. The way in which the pregnancy occurred [spontaneous, in vitro fertilization (IVF) or donation] was documented.

Maternal age was classified into 3 groups (≤25 years, 25-35 years and ≥35 years). At the end of pregnancy, it was documented in which week of gestation and in which way the delivery occurred (vaginal delivery or cesarean section). The laboratory results of the patients were evaluated and also it was checked whether there was anemia. It was evaluated whether there were any pregnancy complications [Hypertensive disorders, gestational diabetes mellitus (GDM), Small for gestational age (SGA), IUGR, low birth weight (<2500gr) and congenital malformation]. In addition, patients who were recommended selective fetal reduction were recorded. Obtained data were recorded and classified, and percentage values were calculated for all groups.

RESULTS

A total of 226 patients with multiple pregnancies were included in the study. Pregnancies of 109 patients were spontaneous (**Table 1**). However, the number of multiple pregnancies after IVF and donation was 116 and 1, respectively. Of 226 patients, 211 were twins, 14 were triplets and one was quadruplet. While monochorionic monoamniotic (MCMA) pregnancy was present in 11 of the twin pregnancies, monochorionic diamniotic (MCDA) pregnancy was observed in 18 of them. In addition, dichorionic diamniotic (DCDA) pregnancy was observed in 182 patients. While 5 out of 14 triplet pregnancies were observed as dichorionic triamniotic (DCTrA), 9 of them were observed as trichorionic triamniotic (TrCTrA). One patient with quadruplet pregnancy was found to be tetrachorionic tetraamniotic (TCTA).

55.7% of multiple pregnancies were older than 35 years (**Table 2**). The percentage of pregnant women under the age of 25 was 14.6%. While 137 (60.6%) of 226 patients were primiparous, 89 (39.3%) patients had previous pregnancies. 20 of the twin pregnancies and 7 of the triplet pregnancies delivered before 25 weeks of gestation. While 45 patients (19.9%) with twin pregnancies delivered after 34 weeks of gestation, no birth was observed in triplets and quadruplets over this week. 202 (89.3%) of all multiple pregnant women were delivered by cesarean section. Anemia (Hb<11mg/dL) was detected in 128 patients with twin pregnancies and 4 patients with triplets (58.4%). Patients with high blood pressure (≥140/90 mmHg) after the 20th week of pregnancy were considered as hypertensive disorder of pregnancy and was found in 28 patients with twins and in 4 patients with triplet pregnancies (14.1%). Patients with high values (fasting glucose ≥ 5.1 mmol/L, 1st hour glucose ≥10 mmol/L, 2nd hour glucose ≥ 8.5 mmol/L) in the 75 g oral glucose tolerance test were considered as GDM. GDM was observed in 41 patients with twin pregnancies and 3 patients with triplet pregnancies (19.4%). Pregnancies with an estimated fetal weight below the 10th percentile according to the gestational week were accepted as SGA and it was observed in 121 twin pregnants (53.5%). In addition, SGA findings were observed in 13 triplets and 1 quadruplet pregnancy. Fetuses with fetal abdominal circumference below the 3 percentile were evaluated as IUGR. While IUGR was detected in 82 multiple pregnancies (36.2%) in total, 76 of them had twin pregnancies and 6 of them had triplets. The number of multiple pregnancies with a birth weight of less than 2500 g was found to be 187 (82.7%) in total. Of these, 172 were twin pregnancies, 14 were triplets, and 1 was quadruplet. Major congenital anomaly of various organs (cardiac, central nervous system, etc.) was observed in 8 (3.5%) pregnant women. Selective fetal reduction was offered to 2 pregnant women with MCDA/major congenital anomaly in a single fetus and 1 pregnant woman with DCTrA/major congenital anomaly in a single fetus, but they did not accept it. Selective fetocide was applied to 4 patients with DCDA and 1 patient with TrCTrA who had major anomaly in one fetus. Fetal reduction was offered to the pregnant woman with quadruplets, but she refused.

DISCUSSION

Increasing use of assisted reproductive techniques and postponing pregnancy to advanced ages have increased the incidence of multiple pregnancy (10,11). In our study, the rate of pregnancy over the age of 35 was 55.7%. We think that this high rate is especially related to pregnant women who have undergone IVF treatment. Also, the high rate of DCDA pregnancies is related to IVF pregnancies.

Table 1. Chorionicity and conception patterns of the patients participating in the study

	Twins (n=211)			Triplets (n=14)		Quadruplets (n=1)
	MCMA	MCDA	DCDA	DCTrA	TrCTrA	TCTA
SP (n)	11	17	67	4	9	1
IVF (n)	-	1	114	1	-	-
Donation (n)	-	-	1	-	-	-
Total (n)	11	18	182	5	9	1

SP; spontaneous pregnancy, IVF; in vitro fertilization, MCMA; monochorionic monoamniotic, MCDA; monochorionic diamniotic, DCDA; dichorionic diamniotic, DCTrA; dichorionic triamniotic, TrCTrA; trichorionic triamniotic, TCTA; tetrachorionic tetraamniotic

Table 2. Demographic characteristics, time/type of delivery and pregnancy complications of patients with multiple pregnancies

	Twins			Triplets		Quadruplets	Total (n=226) (n,%)
	MCMA (n=11)	MCDA (n=18)	DCDA (n=182)	DCTrA (n=5)	TrCTrA (n=9)	TCTA (n=1)	
Maternal age (year)							
<25 (n)	3	6	22	-	2	-	34 (14.6)
25-35 (n)	4	4	52	3	3	1	67 (29.6)
>35 (n)	4	8	108	2	4	-	126 (55.7)
Parity							
Primiparous (n)		6	116	4	6	1	137 (60.6)
Multiparous (n)		12	66	1	3	-	89 (39.3)
Week of birth							
<25 wk (n)	2	4	14	4	3	-	27 (11.9)
25 wk-34 wk (n)	9	14	123	1	6	1	154 (68.1)
>34 wk (n)	-	-	45	-	-	-	45 (19.9)
Type of birth							
Vaginal (n)	2	4	14	2	2	-	24 (10.6)
Cesarean section (n)	9	14	168	3	7	1	202 (89.3)
Anemia (n)	5	9	114	2	2	-	132 (58.4)
Hypertensive disorders	4	5	19	1	3	-	32 (14.1)
GDM (n)	3	6	32	1	2	-	44 (19.4)
SGA (n)	7	8	121	5	8	1	150 (66.3)
IUGR (n)	4	7	65	3	3	-	82 (36.2)
Low birth weight (<2500 gr) (n)	11	14	147	5	9	1	187 (82.7)
Congenital malformation (n)	2	1	4	-	1	-	8 (3.5)
Selective fetal reduction (n)	-	-[a]	4[b]	-[c]	1[b]	-[d]	5 (2.2)

MCMA; monochorionic monoamniotic, MCDA; monochorionic diamniotic, DCDA; dichorionic diamniotic, DCTrA; dichorionic triamniotic, TrCTrA; trichorionic triamniotic, TCTA; tetrachorionic tetraamniotic, IVF; in vitro fertilization, GDM; gestational diabetes mellitus, SGA; Small for gestational age, IUGR; Intrauterine growth restriction. [a]Laser coagulation was recommended to 2 patients in terms of congenital anomalies, but not accepted. [b]Selective fetocide for congenital anomaly. [c]Laser coagulation was recommended to 1 patient in terms of congenital anomaly, but not accepted. [d]Fetal reduction was recommended but not accepted.

Multiple pregnancies continue to pose maternal and fetal risks. The probability of stillbirth is higher than in single pregnancies, so the timing of delivery is important. Premature births increase the potential risk in neonatal outcomes (12,13). Khalil et al. (14) stated that more than half of multiple pregnancies delivered before 37 weeks of gestation, and 15% before 34 weeks of gestation. Similarly, we found in our study that only 19.9% of all multiple pregnancies gave birth after 34 weeks of gestation. The rate of multiple pregnancies resulting in preterm birth between 25 and 34 weeks of gestation was 68.1%. All this increase in the frequency of preterm birth is likely to increase fetal risks as well. SGA or IUGR are also more common in multiple pregnancies and the rate of fetuses with low birth weight was found to be 82.7%.

The mode of delivery in multiple pregnancies is still a matter of debate. Cesarean section is frequently performed when the second fetus is not cephalic (15,16). There are studies indicating that planned cesarean section before 36 weeks of gestation may increase neonatal morbidity (16). However, it is also stated that there is decreased neonatal morbidity after 37 weeks. Again, a similar study showed that planned cesarean section did not lead to a decrease in neonatal morbidity (15). In our study, we found that the rate of cesarean section in all multiple pregnancies was 89.3%. Since the rate of cesarean section is higher in pregnant women who exceed the viability limit above 24 weeks, it increases the rate of cesarean section in all multiple pregnancies. In labors before the fetal viability (<24 weeks), vaginal delivery is generally preferred if there is no maternal risk. There may

be several reasons for this high rate of cesarean section. First of all, it may be possible to take the decision of cesarean section more easily because of malpractice cases. In addition, the center where the study was conducted is a tertiary center and because of that reason, high-risk pregnancies are referred from other hospitals in large numbers. Since vaginal delivery is more risky in these pregnant women, the rate of cesarean section may have been high in our study. Finally, triplet and quadruplet pregnants are also included in this rate. Since cesarean section is indicated in these patients, all of them delivered by cesarean section and as a result of this, the total cesarean section rate increased.

There are articles in the literature evaluating the relationship between GDM and multiple pregnancies. Morikawa et al. (17) did not find a difference between multiple and single pregnancies in terms of GDM. In addition, Bajagain et al. (18) found a similar GDM rate in multiple pregnancies to singleton pregnancies (11.42%). However, in our study group, the incidence of GDM was found to be higher in multiple pregnancies. High maternal age is likely to increase the probability of GDM and we think that the high GDM frequency in our study is related to this. In addition, hypertensive disorders of pregnancy may increase in multiple pregnancies. In the ACOG bulletin, it is stated that the frequency of preeclampsia increases in multiple pregnancies (19). Similarly, Narang et al. (20) reported in their article that hypertensive disorders were seen with a rate of 12.7% in twin pregnancies. In our study, we found that hypertensive disorders of pregnancy were observed more frequently (14.1%) in patients with multiple pregnancies. We think that this result may be related to both advanced maternal age and increased placental volume due to multiple pregnancy.

Finally, when we evaluated the patients in terms of anemia, 58.4% of the patients were found to have maternal anemia. These results were similar to previous literature. Ru et al. (21) reported in their study that the frequency of anemia in multiple pregnancies was higher than in single pregnancies.

Piro et al. (22) found the frequency of congenital anomalies in twin pregnancies as 11%. We found this rate lower in our patient population (3.5%). We think that, the low number of patients participating in the study and the termination of pregnancies with major anomalies in the early stages may explain this low rate.

CONCLUSION

The frequency of multiple pregnancies is increasing and the problems it brings are also increasing. Preterm birth, increased maternal morbidity and increased cesarean section frequency are just a few of the risks that multiple pregnancies increase. We believe that, with this study, we will contribute to the literature about the problems that may arise in multiple pregnancies. These risks can be overcome more easily by knowing the potential risks of multiple pregnancies and with more careful follow-up starting from the early stages of pregnancy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Izmir Tepecik Training and Research Hospital Ethics Committee (Date:2023, Decision no: 2023/02-39).

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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Evaluation of MULBSTA, SOFA, APACHE II scores and hematological parameters as predictors of mortality in COVID-19 pneumonia

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ABSTRACT

Aim: COVID-19 (coronavirus disease 2019) pneumonia is a serious condition with high mortality and morbidity. Tools are needed for effective diagnosis and better prediction of prognosis in the course of this disease. This study aimed to compare the effectiveness of the MuLBSTA (Multilobular infiltration, hypo-Lymphocytosis, Bacterial coinfection, Smoking history, hyper-Tension and Age) score with blood parameters, SOFA (Sequential Organ Failure Assessment), and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, and to investigate its significance in predicting 28-day mortality in patients diagnosed with COVID-19 and followed up in the intensive care unit (ICU).

Material and Method: This study included 312 patients admitted to ICU for COVID-19 infection. SOFA, MuLBSTA and APACHE-II scores of patients were estimated at ICU admission. Demographic data and laboratory results of patients were retrospectively reviewed.

Results: Of the 312 patients included in the study, 58.7% (n=183) were male and 41.3% (n=129) were female. The AUC value was 0.863 for the SOFA score and 0.843 for the MuLBSTA score. The MuLBSTA score was positively correlated with the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), while it was negatively correlated with the lymphocyte-to-monocyte ratio (LMR). Patients were divided into two groups as high-risk and low-risk, considering a cut-off value of 12 for the MuLBTSA score. The survival time of patients with a high-risk MuLBTSA score was 12±0.78 days, while the survival time of patients with a low MuLBTSA score was 22.8±1.3 days.

Conclusion: The combined use of the MuLSBTA score, SOFA score, and NLR after ICU admission for COVID-19 pneumonia will be more effective in predicting mortality.

Keywords: APACHE II score, COVID-19 pneumonia, Neutrophil-to-lymphocyte ratio, MuLBSTA score, SOFA score

INTRODUCTION

Coronavirus disease (COVID-19) is caused by a novel coronavirus now known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (1). This disease caused by the SARS-CoV-2 infection was first reported in Wuhan, China in December 2019 (2). After the rapid spread of the disease, the World Health Organization (WHO) declared SARS-CoV-2 an epidemic and a global pandemic on 30 January 2020 (3).

Patients usually present to the hospital with fever, dry cough, dyspnea, headache, fatigue, and muscle and bone pain. Less common symptoms include sore throat, confusion, productive cough, hemoptysis, diarrhea, nausea, and chest pain. Although many COVID-19 patients are asymptomatic, some patients develop pneumonia. These patients have increased respiratory distress, with 10% of them requiring mechanical ventilation and intensive care admission (4). Signs of pneumonia include decreased oxygen saturation, abnormal blood gas, multifocal opacities, or ill-defined areas of segmental consolidation on chest X-ray or computed tomography (CT). Patients presenting to the hospital late or with severe illness usually suffer from acute respiratory distress syndrome (ARDS), acute respiratory failure, acute kidney injury, and multiple organ failure (4,5).

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The COVID-19 pandemic has caused an extremely significant increase in the global mortality rate. Between 2020 and 2021, COVID-19 resulted in 14.83 million deaths (13.23-16.58) (6). Tools for effective diagnosis and better prediction of prognosis are needed to mitigate the burden of this disease on the healthcare system (7).

The MuLBSTA (Multilobular infiltration, hypo-Lymphocytosis, Bacterial coinfection, Smoking history, hyper-Tension and Age) scoring system, one of the scoring systems used for this purpose, was defined by Guo et al. (8) and has a strong predictive ability for mortality in viral pneumonia. The MuLBSTA scoring system examines a population of patients with characteristics similar to those with COVID-19 pneumonia (9). This scoring system consists of 6 main parameters, including multilobar infiltration on CT, lymphocytopenia, bacterial co-infection, smoking history, hypertension, and age >65 years old. The MuLBSTA score can be calculated for each patient with the values of all parameters. A score of 12 and above has been reported to be significantly associated with higher 90-day mortality (8,9).

The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system is the most widely used disease severity scale in intensive care units (ICUs) worldwide. This system is composed of 12 parameters and is applied within the first 24 hours after ICU admission. A higher APACHE II score represents a more severe illness and a higher risk of in-hospital death (10). The Sequential Organ Failure Assessment (SOFA) score can be calculated at ICU admission and subsequently every 24 hours. This scoring system consisting of 6 parameters is used to assess the condition of patients admitted to ICU. Changes in the SOFA score show a strong correlation with ICU mortality (11).

Various blood parameters such as neutrophil count, lymphocyte count, monocyte count, platelet count, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio are used in the diagnosis, follow-up, and prognosis of infections. These are simple and cost-effective tests that can be used to determine disease severity and clarify the treatment plan (12). Especially the neutrophil-to-lymphocyte ratio has been reported to be a predictor for the presence of in community-acquired pneumonia (13). The lymphocyte-to-monocyte ratio has been reported to have a prognostic value in the diagnosis of respiratory tract infections caused by viral infections associated with Haemophilus influenza (14). Moreover, it is believed that the platelet-to-lymphocyte ratio may be a novel indicator for predicting the prognosis of COVID-19 patients (15). Another study showed that an increase in PCO_2 concentration in COVID -19 patients, together with older age, high APACHE scores, low lymphocyte count, elevated NLR could predict mortality (16).

This study aimed to compare the effectiveness of the MuLBSTA score with blood parameters, and the SOFA and APACHE II scores, which are universally used in intensive care units, and to investigate its significance in predicting 28-day mortality in patients diagnosed with COVID-19 and followed up in ICU.

MATERIAL AND METHOD

The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (Date: 02.12.2022, Desicion No: 582). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Patients who were admitted to the intensive care unit of Burdur State Hospital for COVID-19 infection between July 2020 and September 2022 were included in the study. This single-center study retrospectively reviewed the data of the patients. The study included only those with positive reverse transcription-polymerase chain reaction (RT-PCR) results of nasopharyngeal and tracheal aspirate samples. Of the patients whose data were reviewed in the study, 2 patients under the age of 18 years, 6 pregnant patients, 18 patients with end-stage renal disease, 2 patients with liver failure, 8 patients with active malignancies, 1 patient who received active immunosuppressive therapy after transplantation, 33 patients with less than 24 hours of ICU stay due to death or transfer to the ward, and 26 patients with incomplete data were excluded from the study. A total of 312 patients who met the inclusion criteria were identified for statistics (shown in **Figure 1**).

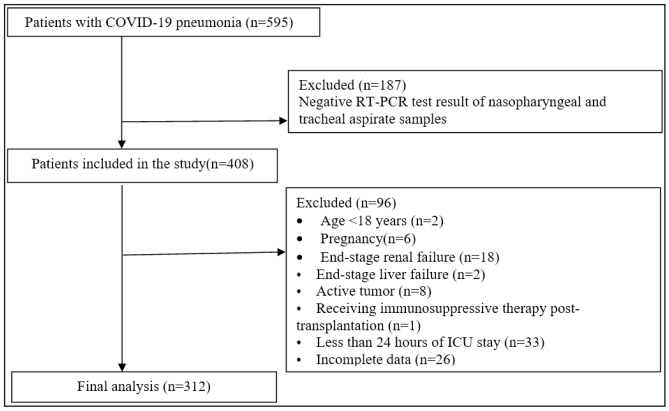

Figure 1. Flow chart of the study.
Abbreviations:COVID-19, coronavirus disease;RT-PCR, Reverse transcription-polymerase chain reaction; ICU, Intensive care unit.

Data Collection and Prognostic Scores

Data including demographic information, medical history, clinical findings, laboratory results, radiological images, and length of ICU stay were collected from

the medical electronic records of patients. Among the laboratory tests performed at ICU admission, leukocyte count, neutrophil count, lymphocyte count, monocyte count, platelet count, C-reactive protein (CRP), procalcitonin (PCT), ferritin, and D-dimer data were recorded. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, the lymphocyte-to-monocyte ratio (LMR) by dividing the absolute lymphocyte count by the absolute monocyte count, and the platelet/lymphocyte ratio (PLR) by dividing the absolute platelet count by the absolute lymphocyte count. SOFA scores (11), MuLBSTA scores (8), and APACHE II (10) scores were determined using standardized forms within 24 hours of admission. In addition, the length of ICU stay, requirement for mechanical ventilation, and time until death were recorded.

Statistical Analysis

Categorical variables were presented as percentages and frequencies. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to check whether continuous variables followed a normal distribution. Normally distributed continuous variables were presented as mean±standard deviation, while non-normally distributed continuous variables were presented as median and interquartile range (IQR). The chi-square test was used to compare categorical variables between groups. In the comparison of continuous variables, the independent samples t-test was used for normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. The Receiver operating characteristic (ROC) curve obtained by calculating the sensitivity and specificity for mortality was used to assess the performance of the tested scores. Youden's index was used to determine the optimal cut-off value based on the ROC analysis results. Survival analysis was carried out using the Kaplan-Meier method. Factors affecting survival were investigated by log-rank test. Spearman's correlation coefficient was calculated and reported to reveal the degree of association between the continuous variables included in the study. Analyses were conducted with the SPSS version 22.0 software package.

RESULTS

Of the patients included in the study, 58.7% (n=183) were male and 41.3% (n=129) were female. The median age of the study group was 75 years (IQR=19 years). During the intensive care follow-up, 66.3% (n=207) of our patients died, while 33.7% (n=105) were discharged. The comparison of these patients in terms of demographic characteristics, clinical characteristics, and laboratory results is shown in **Table 1**.

Table 1. Comparison of demographic characteristics, clinical characteristics and laboratory results of patients

	Survival Group (n=105)	Mortality Group (n=207)	p value
Age (years)	71 (62-81)	78 (67-85)	0.002*
Sex			0.904**
Male, n (%)	61 (33.3%)	122 (66.7 %)	
Female, n (%)	44 (34.1 %)	85 (65.9 %)	
CRP (min-max)	87.5 (51.5-136.5)	110 (60-178)	0.018*
Procalcitonin (min-max)	0.15 (0.03-0.60)	0.41 (0.14-1.37)	<0.001*
Ferritin (min-max)	399 (198.5-690)	550 (312-1051)	<0.001*
D-dimer (min-max)	502 (294.5-1182)	804 (390-1463)	0.006*
APACHE-II (min-max)	17 (15-21)	20 (17-25)	<0.001*
SOFA (min-max)	6 (5-8)	9 (8-11)	<0.001*
MuLBSTA (min-max)	11 (9-13)	15 (15-18)	<0.001*
NLR (min-max)	9.19 (5.41-14.6)	17.48 (11.85-25.11)	<0.001*
LMR (min-max)	2.15 (1.36-3.15)	1.44 (0.92-2)	<0.001*
PLR (min-max)	243.1 (159.2-369.8)	351.31 (243.3-481.4)	<0.001*

*Mann-Whitney U test, **Fisher's exact test
Abbreviations: CRP, C-reactive protein; APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

The ROC analysis results for APACHE II score, SOFA score, MuLBSTA score, NLR, LMR, and PLR are shown in **Table 2**. The AUC value was 0.863 for the SOFA score and 0.843 for the MuLBSTA score. The sensitivity and specificity of a cut-off value of 7.5 for the SOFA score to predict survival were 0.81 and 0.72, respectively, while

Table 2. Optimal cut-off values and ROC analysis results for APACHE II score, SOFA score, MuLBSTA score, NLR, LMR, and PLR

Risk Factor	AUC	95% CI	Cut-off	p-value	Sensitivity %	Specificity %
APACHE II score	0.675	0.612-0.734	17.50	0.000	0.73	0.54
SOFA score	0.863	0.820-0.906	7.50	0.000	0.81	0.72
MuLBSTA score	0.843	0.799-0.888	12.50	0.000	0.86	0.58
NLR	0.730	0.670-0.790	9.24	0.000	0.85	0.51
LMR	0.330	0.266-0.394	1.44	0.000	0.51	0.32
PLR	0.646	0.580-0.712	265.27	0.000	0.71	0.57

Abbreviations: APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio;AUC, area under the curve; CI, confidence interval.

the sensitivity and specificity of a cut-off value of 12.5 for the MuLBSTA score were 0.86 and 0.58, respectively. **Figure 2** and **Figure 3** show the ROC curves plotted to estimate ICU mortality.

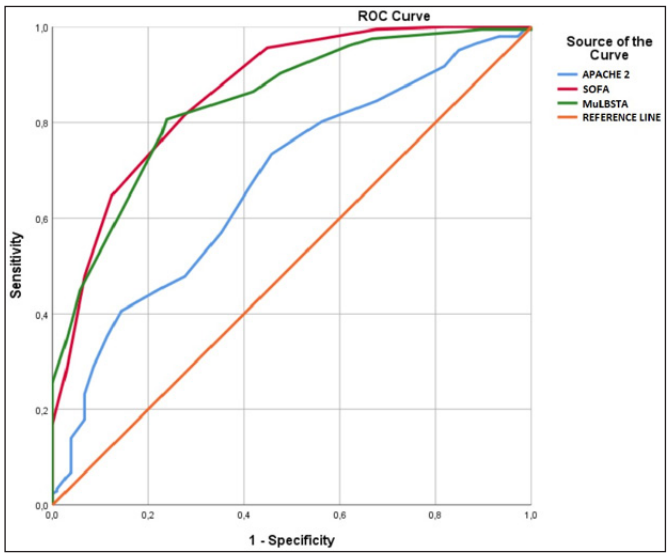

Figure 2. ROC analysis for APACHE II score, SOFA score, and MuLBSTA score.
Abbreviations: APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment.

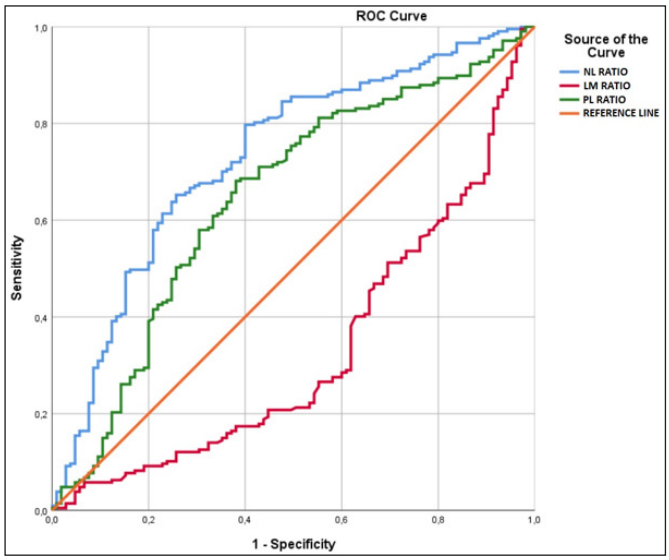

Figure 3. ROC analysis for NLR, LMR and PLR.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

NLR was positively correlated with CRP (r=0.152, p=0.007), procalcitonin (r=0.189, p=0.001), ferritin (r=0.159, P=0.005), D-dimer (r=0.161, p=0.004), SOFA score (r=0.199, p=<0.001), APACHE II score (r=0.147, p=0.009), and MuLBSTA score (r=0.342, p<0.001). LMR was negatively correlated with D-dimer (r=-0.139, p=0.039), SOFA score (r=-0.149, p=0.008), APACHE II score (r=-0.111, p=0.05), and MuLBSTA score (r=-0.234, p<0.001). On the other hand, PLR was positively correlated with only the MuLBSTA score (r=0.251, p<0.001). These results showed a positive correlation between the MuLBSTA score and NLR, PLR, and a negative correlation between the MuLBSTA score and LMR. The results of correlations between the variables are shown in **Table 3**.

Table 3. Correlations between variables

	NLR		LMR		PLR	
	r	p-value	r	p-value	r	p-value
CRP	0.152	0.007	0.036	0.52	0.075	0.187
Procalcitonin	0.189	0.001	-0.008	0.89	-0.043	0.448
Ferritin	0.159	0.005	-0.88	0.119	-0.006	0.917
D-dimer	0.161	0.004	-0.139	0.014	0.039	0.493
SOFA	0.199	<0.001	-0.149	0.008	-0.05	0.378
APACHE II	0.147	0.009	-0.111	0.05	0.025	0.661
MuLBSTA	0.342	<0.001	-0.234	<0.001	0.251	<0.001

Abbreviations: CRP, C-reactive protein; APACHE-II, The Acute Physiology and Chronic Health Evaluation; SOFA, The Sequential Organ Failure Assessment; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio.

Patients were divided into two groups as high-risk and low-risk, considering a cut-off value of 12 for the MuLBTSA score. The survival time of patients with a high-risk MuLBTSA score was 12±0.78 days, while the survival time of patients with a low-risk MuLBTSA score was 22.8±1.3 days. There was a statistically significant difference in survival between the groups with high and low-risk MuLBSTA scores (p<0.001). The Kaplan-Meier (K-M) survival curves for high-risk and low-risk groups are shown in **Figure 4**.

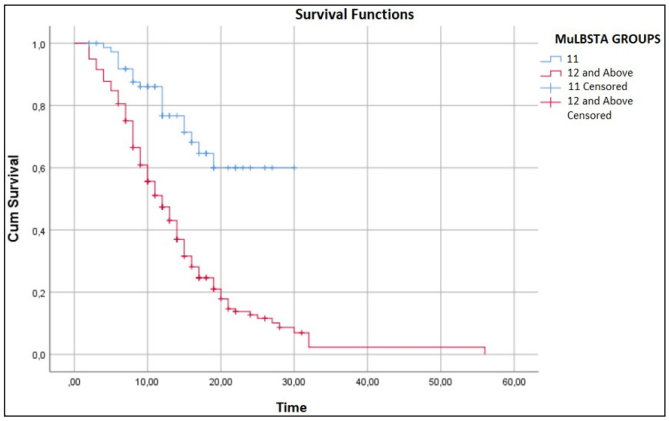

Figure 4. Kaplan-Meier survival curve of patients classified by MuLBSTA score.

DISCUSSION

COVID-19 has emerged as a disease with very high mortality and morbidity, causing very serious problems on a global scale. COVID-19 pneumonia has seriously increased the workload in intensive care units during the pandemic. During this period, some scoring systems and indicators have come to the fore in order to reduce the burden of these patients on the healthcare system, to select patients to be admitted to ICU, and to predict mortality.

In general, smokers, elderly population, patients with cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension, cancer or obesity have an increased risk of death due to SARS-CoV-2 infection (17). The prognosis of a disease becomes extremely important when so many factors play a role. The MuLBSTA scoring system is one of the tools that can help physicians in this decision-making process (18).

Elderly patients with COVID-19 have a higher mortality rate due to the high rate of symptomatic infection (19). Studies have confirmed the association between increased age and death in COVID-19 patients (19,20). Our study demonstrated a correlation between advanced age and mortality in COVID-19 disease (p=0.002).

Although COVID-19 infection may be a mild flu-like illness or be asymptomatic in most patients, a small proportion of patients may develop severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and even death. Various laboratory markers have been proposed for risk stratification in these patients. There is increasing evidence that features of hyperinflammation consisting of elevated serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia are seen in critically ill patients (7). A study by Cellina et al. (21) reported a significant increase in acute phase reactants such as CRP and D-dimer of patients with COVID-19 pneumonia in the mortality group. Similarly, in their meta-analysis investigating mortality factors for COVID-19 pneumonia, Li Zhang et al. (22) reported statistically higher CRP, PCT, and D-dimer levels in deceased patients than in the survival group.The results of our study also showed elevated levels of acute phase reactants, including CRP, PCT, D-dimer, and ferritin in the mortality group.

APACHE II and SOFA scores are well-known scoring systems that have been used for many years to evaluate critically ill patients and predict their mortality (23). Simple blood markers of NLR, LMR, and PLR are new biomarkers of systemic inflammation that are closely related to immune response (24). A study evaluating COVID-19 pneumonia in ICU patients reported statistically significantly higher APACHE II and SOFA scores in the deceased group than in the survival group (23). In their study investigating COVID-19 mortality, Citu et al. (25) reported a difference in NLR and MLR but no difference in PLR between the mortality and survival groups. Our study revealed a significant difference in APACHE II, SOFA scores, and NLR, LMR, and PLR values between the mortality group and the survival group.

A complete blood count is the cheapest, most accessible, and fastest diagnostic test among the markers that can be used. White blood cell, neutrophil, lymphocyte, and platelet counts and NLR, LMR, and PLR derived from these parameters provide us with rich information. There are studies showing that these hematological parameters especially predict inflammation (12,26). A study by Yanga et al. (12) evaluating NLR, LMR, and PLR to predict mortality of COVID-19 pneumonia by ROC analysis reported the AUC values as 0.841, 0.265, and 0.784, respectively. In our study, the AUC values for NLR, LMR, and PLR were found to be 0.730, 0.330, and 0.646, respectively. Based on our data, NLR and PLR were found to have a prognostic value, while LMR had no prognostic significance because its AUC value was less than 0.50. We are of the opinion that these simple biomarkers derived from hematological tests can be evaluated to predict the prognosis of COVID-19.

In our study, the AUC value was 0.863 for the SOFA score, 0.843 for the MuLBSTA score, and 0.673 for the APACHE II score. The sensitivity and specificity of the SOFA score to predict survival were 0.81 and 0.72, respectively, while the sensitivity and specificity of the MuLBSTA score were 0.86 and 0.58, respectively. In their study, Fayed et al. (27) reported an AUC value of 0.883 for the SOFA score in COVID-19 pneumonia, stating that it is a good predictor of mortality. Gowda et al. (28) reported an AUC value of 0.766 for the SOFA score, emphasizing that it is a better predictor than the APACHE2 score. Garcia et al. (29) found an AUC value of 0.777 for the MuLBSTA score to predict mortality in COVID-19 pneumonia, with a sensitivity of 0.683. In our study, the AUC value for the MuLBSTA score was 0.843, with a sensitivity of 0.86, while the AUC value for the SOFA score was 0.863, with a sensitivity of 0.81. Based on our results, we believe that the MuLBSTA and SOFA scores are better predictors of mortality than the APACHE II score.

A study by Peng et al. (30) evaluating the diagnostic data of hematological parameters in COVID-19 pneumonia reported a positive correlation between NLR and the MuLBSTA score. In our study, NLR was positively correlated with MuLBSTA and SOFA scores.

Guo et al. (8) divided the patients into two groups according to their MuLBSTA scores and classified those with a score of 0-11 as the low-risk group (mortality rate of 5.07%) and those with a score of 12-22 as the high-risk group (mortality rate 33.92%) and reported that the MuLBSTA score was a good predictor of prognosis. In a study by Preetam et al. (17), they compared the 14-day risk of mortality in both groups and showed an strong association in patients with a MuLBSTA score ≥12. Another study showed that COVID-19 patients with a

higher admission MuLBSTA score had a higher risk of death. In this study, it was shown that the ≥12 MuLBSTA score had a specificity of 89.5% and a sensitivity of 100% in predicting mortality (31). Our study revealed a statistically significant difference in survival between the groups with high and low-risk MuLBSTA scores ($p<0.001$).

There are several limitations to the present study. First of all, the study is a single-center study. The second limitation is the retrospective design of the study. The third limitation is the MuLSBTA score, which was originally defined as a predictor of 90-day mortality. In our study, 28-day mortality was evaluated due to the difficulty in reaching patients during the pandemic.

CONCLUSION

COVID-19 pneumonia is a global public health threat that causes very serious health problems due to its spread rate and course. It has been clearly seen during the pandemic that early diagnosis and prediction of prognosis are very important. These prognostic predictions are also gaining importance in intensive care clinics. The MuLBSTA scoring system is a good tool to predict the mortality of COVID-19 pneumonia. Especially patients with a score ≥12 are associated with poor prognosis. SOFA, a conventional intensive care scoring system, also provides significant guidance in this respect. NLR obtained from hematological parameters also yielded significant results. The combined use of the MuLSBTA score, SOFA score, and NLR after ICU admission in COVID-19 pneumonia will be more effective in predicting.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (Date: 02.12.2022, Desicion No: 582).

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 pregnant women and their spouses' belief in sexual myths during pregnancy, relationship satisfaction and sexual satisfaction

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ABSTRACT

Aim: Pregnancy, birth and post-partum period is an important process in which many physiological, psychological and social changes are experienced by mothers and fathers. Pregnancy is also one of the periods when sexuality is most affected, and sexual dysfunctions are common during this period. The aim of this study is to investigate the sexuality and sexual myths of pregnant women and their partners.

Material and Method: This research was conducted in an university hospital in Turkey with a total of 128 participants, 77 pregnant women and 51 spouses who agreed to participate.

Results: There was a statistically significant relationship in terms of working status, having a history of miscarriage in the family, and sexual knowledge adequacy before marriage. Men's employment rate and pre-marital sexual knowledge adequacy status were higher than women. A statistically significant difference has been achieved in the "Sexuality/Attractivess" sub-dimension in Sexual Myths During Pregnancy Scale (SMDPS) and the "Avoidance" and "Communication" sub-dimensions in Glombock - Rust sexual satisfaction Scale (GRSSS). An inverse low correlation between sexual myths during pregnancy and GRSSS in men and low-level lineer relationship between GRSSS and Relationship Satisfaction Scale(RSSS) scores in women are detected.

Conclusions: Exaggerated, false beliefs that are considered true but not actually related to sexuality, sexual myths negatively affect the relationship of couples. The prevalence of sexual myths during pregnancy will decrease and the impact on the quality of sexual life during pregnancy will be minimized by obtaining consultancy services.

Keywords: Pregnancy, sexuality, sexual satisfaction, myth, relationship satisfaction

INTRODUCTION

Pregnancy, birth and post-partum period is an important process in which many physiological, psychological and social changes are experienced by mothers and fathers (1). Pregnancy is also one of the periods when sexuality is most affected, and sexual dysfunctions are common during this period (2).

Despite the age of information and technology, common causes of sexual dysfunction in women include sexual inexperience or lack of knowledge, growing up in a conservative society, deficiencies in sexual education, and false beliefs and myths about sexuality (3). These factors affect the sexual attitudes and behaviors of couples during a sensitive period such as pregnancy, causing negativity in the sexual life of couples (4).

Sexual myths are mythical beliefs that have not been scientifically clarified in terms of sexuality and have no evidence for individuals. Sexual myths are among the factors that can affect general public health, as they affect the sexual process and quality of sexual life. In addition, common beliefs and attitudes may differ both between cultures and regionally. These differences are based on individuals, age, gender, education, family type varies between (5).

It was stated that false beliefs of pregnant women negatively affect sexual function, and it was determined that less sexual intercourse, less desire and less arousal occurred in pregnant women with false beliefs in this process (6). Fear of harming the fetus or pregnancy is among the reasons

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for this decrease (7). Although sexual intercourse has been proven to be safe in all trimesters, the widespread fear of harming the fetus/pregnancy is explained by the prevalence of sexual myths and lack of sexual knowledge (8). As can be seen, sexual myths still maintain their prevalence today, and with the continuing lack of sexual knowledge, sexual myths affect the quality of sexual life.

Almost all of the sexual myths consist of negative attitudes that sexual intercourse during pregnancy will be harmful, and these attitudes also negatively affect the quality of sexual life. Pregnant women avoid sexual intercourse due to the fear of harming the fetus during pregnancy and the thought that sexual intercourse will cause miscarriage and bleeding, and this situation negatively affects the quality of sexual life (9,10).

For this reason, it is important to reveal the attitudes and knowledge levels of pregnant women and spouses towards sexual myths (11). Although there were studies examining sexual myths in previous literature, no article investigating the sexuality and sexual myths of pregnant women and their partners have been published. Regarding this purpose we assume that our research will be an important step in determining the myths about sexuality of pregnant women and their pregnant spouses and identifying possible sexual problems they experienced.

The aim of this study was to elucidate false information, attitudes and beliefs of pregnant women and their partners about sexual life during pregnancy. Additionally, determinining the myths on the relationship between relationship satisfaction and sexual functions and providing training and consultancy in order to contribute to a healthy sexual life and healthy family structure would be positioned as an important asset.

MATERIAL AND METHOD

The study was carried out with the permission of Balıkesir University Health Sciences Non-Interventional Researches Ethics Committee (Date: 22.03.2022, Decision No: 2022/34). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This research has been conducted as a survey within 128 individuals who have applied to our institution in Turkey.

77 pregnant women and 51 spouses over 18 years old and at least graduated from primary school has been enrolled within the scope of this study. Patients diagnosed with mental retardation and psychotic disorder, individuals with primary or acquired neurological diseases that may affect cognitive abilities (stroke, dementia, head trauma, cranial operation) and those with ongoing alcohol or substance abuse were excluded. An informed consent form was obtained from the participants who agreed to participate in the study. Sexual Myths During Pregnancy Scale(SMDPS), Glombock - Rust sexual satisfaction Scale(GRSSS), Relationship Satisfaction Scale(RSSS) were applied.

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage were given for categorical data, and median, minimum and maximum descriptive values for continuous data. "Mann Whitney U Test" was used for comparisons between groups, and "Chi-square or Fisher's Exact Test" was used for comparison of categorical variables. "Spearman Correlation Analysis" was used to evaluate the relationship between continuous variables. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

Within the scope of the study, a total of 128 individuals, 51 (39.8%) male and 77 (60.2%) female, were included in the evaluation. The distribution of the socio-demographic characteristics of the participants according to their gender was given in **Table 1**. When the table was examined, it was seen that there was a statistically significant relationship in terms of working status, having a history of miscarriage in the family and sexual knowledge adequacy before marriage ($p<0.05$). It was seen that men's employment rate and pre-marital sexual knowledge adequacy status were higher than women.

The distribution of sexual myths during pregnancy, Glombock - Rust sexual satisfaction and relationship satisfaction scale scores by gender of the participants were elaborated in **Table 2**. When the table was examined, it was seen that there was a statistically significant difference between the two groups in the "Sexuality/ Attractivess" sub-dimension and the "Avoidance" and "Communication" sub-dimensions ($p<0.05$). The median scale score of women was higher than men in significant parameters.

Sexual myths during pregnancy, Glombock - Rust sexual satisfaction and relationship satisfaction scale scores have been analyzed via Spearman correlation analysis (**Table 3**). When the table was examined, it was seen that there was an invers low correlation between sexual myths during pregnancy and Glombock - Rust sexual satisfaction scores in men, and a lineer low-level relationship between Glombock - Rust sexual satisfaction and relationship satisfaction scale scores in women ($p<0.05$).

Table 1. Distribution of socio-demographical characteristics of individuals by gender

Characteristics	Total (N=128)	Male (n=51)	Female (n=77)	p-value
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Age, years	29 (18-46)	30 (24-46)	29 (18-42)	
Residential area				0.617
City	82 (64.1)	34 (66.7)	48 (62.3)	
Village – town	46 (35.9)	17 (33.3)	29 (37.7)	
Working status	79 (61.7)	48 (94.1)	31 (40.3)	<0.001
Marriage age				0.134
≤18 years	1 (0.8)	0 (0)	1 (1.3)	
18 – 25 years	66 (51.6)	20 (39.2)	46 (59.7)	
26 – 30 years	44 (34.4)	21 (41.2)	23 (29.9)	
31 – 35 years	13 (10.2)	8 (15.7)	5 (6.5)	
≥36 Years	4 (3.1)	2 (3.9)	2 (2.6)	
Duration of marriage				0.817
0 – 1 years	29 (22.7)	12 (23.5)	17 (22.1)	
1 – 3 years	45 (35.2)	20 (39.2)	25 (32.5)	
3 – 5 years	12 (9.4)	4 (7.8)	8 (10.4)	
5 years or above	42 (32.8)	15 (29.4)	27 (35.1)	
Way of conceving				0.585
Natural	113 (88.3)	44 (86.3)	69 (89.6)	
With treatment	15 (11.7)	7 (13.7)	8 (10.4)	
Previous miscarriage	28 (21.9)	6 (11.8)	22 (28.6)	0.042
Sexual knowledge adequacy before marriage	104 (81.3)	47 (92.2)	57 (74)	0.019
Sexual guilt during pregnancy	7 (5.5)	2 (3.9)	5 (6.5)	0.702
Frequency of sexual intercourse during pregnancy				0.176
≤ 3/months	80 (62.5)	36 (70.6)	44 (57.1)	
≥ 4 /months	48 (37.5)	15 (29.4)	33 (42.9)	
Sexual knowledge adequacy during pregnancy	97 (75.8)	36 (70.6)	61 (79.2)	0.365
Previous sexual disorder	5 (3.9)	0 (0)	5 (6.5)	0.156

Table 2. Distribution of survey scores by gender of individuals

Chractersitics	Total (N=128)	Male (n=51)	Female (n=77)	p value
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Sexual myths during pregnancy				
Pregnancy & sexual life	14 (5-21)	14 (6-21)	14 (5-21)	0.578
Concern for baby	10.5 (7-33)	9 (7-28)	11 (7-33)	0.555
Sexuality/attractivess	8 (5-20)	7 (5-20)	9 (5-20)	0.008
Concern for pregnancy	16 (8-32)	16 (8-32)	16 (8-32)	0.606
Glombock - Rust sexual satisfaction scale				
Touching	2 (0-14)	1 (0-12)	3 (0-14)	0.062
Avoiding	1 (0-12)	1 (0-9)	2 (0-12)	0.024
Satisfaction	3 (0-12)	3 (0-12)	3 (0-12)	0.381
Frequency	3 (0-7)	3 (0-6)	3 (1-7)	0.387
Communication	3 (0-8)	2 (0-8)	3 (0-8)	0.008
Relationship satisfaction scale	40,5 (19-42)	41 (25-42)	40 (19-42)	0,408

Table 3. Distribution of the relationship between the survey scores of the individuals by gender

Spearman's RHO			SMDPS	GRSSS	RSSS
Male	SMDPS	Correlation coefficient	1.000	-0.406	-0.106
		p-value	-	0.003	0.460
		N	51	51	51
Female	GRRSS	Correlation coefficient	0.153	1.000	0.417
		p-value	0.184	-	<0.001
		N	77	77	77

SMDPS:Sexual Myths During Pregnancy Scale, GRSSS:Glombock - Rust Sexual Satisfaction Scale, RSSS:Relationship Satisfaction Scale

DISCUSSION

Sexual attitudes and behaviors are shaped by environmental factors such as social value judgments, laws, history, lifestyle, traditions, religious belief, culture and moral attitudes, gender roles, and social status (12). In a study, it was stated that the sexuality perception of couples, cultural norms, parenting thoughts, lack of knowledge, and negative thoughts about sexual life had a negative effect on sexuality during pregnancy (13).

Physiological situations such as nausea and vomiting, weakness and tiredness experienced during pregnancy are among the factors affecting sexuality in pregnant women. Most pregnant women think that their sexual functions are decreased in this period. Due to these problems, it is inevitable to experience some difficulties between spouses in the field of sexuality as well as in all areas of life (14).

Changes in the body image of the pregnant also negatively affect the sexual life during pregnancy. Especially in the later stages of pregnancy, pregnant women may be worried due to weight gain, enlargement of the abdomen and breasts, thickening of the waist, and darkening of the vagina color due to pigmentation (15). Women also experience the fear of losing their sexual attractiveness, love and interest of their spouses during pregnancy (16). This situation was also supported by previous studies, and women stated that the sexual intercourse they experienced during pregnancy was initiated by their husbands, they had sex to prevent their husbands' infidelity and they could not have an orgasm (17 – 19). In our study, the sexual myths during pregnancy parameters and Glombock - Rust sexual satisfaction and relationship satisfaction scale scores by gender of the participants were statistically significantly different between the two groups in the "Gender/Attraction" sub-dimension and the "Avoidance" and "Communication" sub-dimensions.

Although there are no biological differences in men during pregnancy, it is known that they also show some psychological reactions in adapting to the new role (20). Therefore, pregnancy is considered as an event that affects the psychological state of men. Acceptance of pregnancy in men includes not only the acceptance of the baby but also the changing state of the mother. In this case, men try to adapt to pregnancy by being more emotionally involved with their wives, keeping their wives in the foreground, and searching for pregnancy-specific information, and they feel happy and proud about being a father (21,22).

In the second half of pregnancy, father candidates become more aware of the pregnancy and begin to accept the baby thoroughly. Couples do not change their routine sexual lives due to the fact that sexuality is not affected much in the second trimester, thus increasing their interdependence (23). However, men who feel the fetus fully due to the enlargement of the uterus in the future, bargain with their feelings and emotions about having sex not only with their spouse, but also with the woman who will be the mother of their baby. Some men, on the other hand, believe that touching a pregnant woman, even if they want sexual intercourse with their wives, is defiling something sacred. Others believe that it is immoral to have sex with a pregnant woman and therefore avoid sexual intercourse. On the other hand, most men think that touching their wives during pregnancy increases happiness and peace (22). During this period, couples should maintain a healthy relationship in order to develop mutual emotional bonds and close physical attraction, as well as to share sexual satisfaction and meet each other's sexual needs (24).

Despite this, the results of some studies show that sexual intercourse can be most comfortable in the first trimester. Pauleta et al. (25) found in their study with pregnant women that they had sexual intercourse most frequently in the first trimester and that their sexual desire and satisfaction in this trimester did not change compared to the pre-pregnancy period. On the contrary, Zahumensky et al. (26) stated that the least sexual involvement among the three trimesters was the first trimester, however, as the pregnancy progressed, sexual dysfunctions increased and coitus accompanied by orgasm decreased.

Libido is affected by physical and mental changes during pregnancy. Increases and decreases in libido can be seen at various stages of pregnancy. While the variability in libido is quite evident in the mother-to-be, it is milder or not observed in the father-to-be (27). Frequency of sexual intercourse is an important parameter that informs us about the level of libido. The common view in many studies on this issue is that the frequency of sexual intercourse decreases significantly during pregnancy when compared to the pre-pregnancy period (28).

In a meta-analysis of 59 studies dealing with pregnancy and the postpartum period, it was concluded that the frequency of sexual intercourse slightly decreased or even did not change in the first trimester, it was very variable in the second trimester, and decreased significantly in the third trimester (29).

When libido is examined in terms of initiating sexual activity, it is seen that this activity is usually initiated by the male partner before and during pregnancy. Naim and Bhutto (30) stated that mostly men initiate sexual intercourse during pregnancy and rarely women in an early publication. In the study of Gökyıldız and Beji (19) on 150 Turkish pregnant women, it was shown that the initiator of sexual intercourse during pregnancy was generally answered as male. It is understood that the male

partner is significantly dominant in initiating sexuality before and during pregnancy. The reason for this may be the cultural structure of the society and the biological structure of the woman (22).

Sexual intercourse resulting in orgasm has been examined in many studies and it has been determined that it decreases significantly before pregnancy compared to the gestational period (28). In this study we have found an inverse low correlation between sexual myths during pregnancy and Glombock - Rust sexual satisfaction scores in men, and a lineer low-level relationship between Glombock - Rust sexual satisfaction and relationship satisfaction scale scores in women.

From this point of view, it is possible to say that the quality of sexual life is among the factors affecting the quality of life. Scientific explanation of sexual myths during pregnancy and including sexual myths during pregnancy among the topics to be emphasized while providing consultancy services will enable individuals to access accurate information, and thus, the rapidly spreading sexual myths during pregnancy will leave their place to scientifically based information (22). In our study it was determined that men's employment rate and pre-marital sexual knowledge adequacy status were higher than women, which was an expected finding of our geography.

The prevalence of sexual myths during pregnancy will decrease and the impact on the quality of sexual life during pregnancy will be minimized by obtaining consultancy services on how sexual life will take place during pregnancy and obtaining information from the right sources. At this stage nurses should give priority to issues related to sexuality during pregnancy, because throughout history, the relationship between pregnancy and sexuality has been influenced by the existence of cultural stereotypes, misperceptions, myths and taboos (22).

The strength of this research could be attributed to the idea that although there were studies examining sexual myths in the literature, this was the first study that comparatively investigated the sexuality and sexual myths of pregnant women and their partners.

CONCLUSION

The meaning attributed to the concepts of sexuality and sexual health is significantly influenced by religious rules, taboos and traditions. It is thought that sesxual myths about pregnancy may have an effect on sexual satisfaction and relationship satisfaction. Providing counseling services will reduce the prevalence of sexual myths during pregnancy and increase the quality of sexual life.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Health Sciences Non-Interventional Researches Ethics Committee (Date: 22.03.2022, Decision No: 2022/34).

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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Retrospective analysis of 102 neonatal cases hospitalized with diagnosis of the ongoing phenomenon of neonatal period: hypernatremic dehydration

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ABSTRACT

Aim: The aim of this study was to examine the prevalence of hypernatremic dehydration (HD) among term neonates admitted to a tertiary care unit over a three-year period and to identify mother and neonate related risk factors associated with HD.

Material and Method: Medical records of 102 term babies and their mothers were analyzed retrospectively. The gender, weight at birth, type of birth, postnatal day of diagnosis, weight and weight loss percentage at diagnosis, season and presenting complaint upon admission, feeding with human milk/formula/mixed, laboratory findings, usage of antibiotics as well as maternal age, parity, residence, level of education and presence of smoking were recorded. Serum sodium (Na) levels, severity of dehydration, age on admission, and length of stay in the neonatal intensive care unit (NICU) were recorded along with any significant effect of maternal demographic properties, residence, season, gender, and type of birth.

Results: The average Na levels were found to be 152.1±4.2 mEq/L (max:166 mEq/L). Mild, moderate and severe hypernatremia were found in 34 (33%), 62 (61%) and 6 (6%) patients, respectively. More weight loss was observed in neonates born via cesarean section vs. vaginal delivery (12.8±3.0% vs. 11.6±3.5%, p=0.01). Higher serum Na levels (153.9±4.86 mEq/L vs. 151±2.34 mEq/L, p=0.008) and a greater median age at admission (4.5 [IQR4-6]) days vs. 3 [IQR3-4]) days, p=0.03) were reported for neonates born to mothers residing in rural/suburban vs. urban areas. Serum Na levels were not different based on the mother's level of education or parity (p=0.96 and p=0.29, respectively). There was no difference in serum Na levels (p=0.05) but the percentage of weight loss was higher when the mother smoked (14.3±3.8% vs. 11.7±3.1%, p=0.003). Serum Na and glucose levels were lower, antibiotics usage rates, and prevalence of mixed feedings were higher in early term infants (p=0.01, p=0.002, p=0.04 and p=0.04, respectively). Males had higher creatinine levels (0.89±0.27 mg/dl vs. 0.78±0.28 mg/dl, p=0.005), but there was no difference between the sexes in terms of day of admission, percentage of weight loss, or length of stay in NICU.

Conclusion: Hypernatremic dehydration is a significant and increasingly prevalent problem of neonatal period. Serum Na levels and severity of dehydration in neonates may be affected by the type of birth, mother's smoking status, residence and early term birth. Counseling on breastfeeding, education of health professionals and caregivers on the signs and symptoms of dehydration, and monitoring of body weight are essential for the prevention, diagnosis, and treatment of HD.

Keywords: Newborn, dehydration, hypernatremia, breastfeeding, weight loss

INTRODUCTION

Breastfeeding is the best and most accepted way of feeding for all neonates with proven health benefits and neonates should only be breastfed in the first 6 months of life (1). However, insufficient breastfeeding, lactation failure and as a result breastfeeding malnutrition may end with dehydration in some of the neonates (2). literature added

Dehydration can be classified according to the serum osmolality as isotonic, hypotonic and hypertonic, as the latter being most dangerous. Neonatal hypernatremia is defined as serum sodium (Na) levels greater than 145mEq/L (3) and is subdivided as mild (145-149 mEq/L), moderate (150-159 mEq/L) and severe (>160 mEq/L) (4). Hypernatremic dehydration (HD) is a well-known, historical and ongoing entity of the neonatal period, but the incidence is reported to be increasing in last two decades, owing to increased awareness of the disease and its complications and promotion of breastfeeding as the predominant form of newborn feeding in accordance with baby-friendly hospital initiative policies (5).

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The body and skin characteristics of newborns make them more susceptible to developing HD. The immaturity of the skin barrier, increased extrarenal losses due to greater surface area and decreased capacity of urinary concentration are the accused mechanisms in development of hypernatremia (6). Causes of HD in neonatal period are low fluid intake (hypoalimentation), increased insensible water loss, gastrointestinal losses and renal free water loss in excess of Na, or combination of these (7).

In the first few days of life, breastfeeding can lead to a mild but tolerable dehydration. However, premature hospital discharges without effective lactation support, education, and adequate follow-up, lactation failure with ineffective milk production, and inadequate or suboptimal breastfeeding may result in HD (8,9). In addition, decreased feeding frequency due to neonatal and/or maternal factors, such as infection, stress, mastitis, or flat/inverted nipples, may be superimposing factors in the development of a more severe dehydration and hypernatremia (10,11). Approximately 35% of exclusively breastfed neonates who lost more than 10% of their birth weight in the first few days were found to have hypernatremia (12).

In HD, the clinical manifestations of dehydration, such as tachycardia, decreased skin turgor, and hypotension, are less common because extracellular fluid and plasma volumes are relatively preserved, but intravascular shrinkage occurs (7). Due to the less pronounced signs of dehydration and the absence of routine screening of serum Na levels in the first days of life, dehydration can be difficult to diagnose and is probably more common than reported (13). If neonatal HD is not diagnosed and treated promptly, it can be fatal. It can lead to transaminitis, metabolic acidosis, seizures, venous sinus thrombosis, pontine myelinolysis, permanent brain damage, disseminated intravascular coagulation, acute kidney injury, and even death (14). Both the condition and its complications, as well as the rapid treatment of hypernatremia, may result in severe injury.

The aim of the present study was to examine the clinical characteristics of neonates diagnosed with HD and hospitalized in the neonatal intensive care unit (NICU), as well as to search for any association between maternal-neonatal risk factors and serum Na levels, severity of dehydration, age at admission, and length of NICU stay.

MATERIAL AND METHOD

Ethics approval for the study was granted by the İstanbul Medipol University Non-Interventional Researches Ethics Committee (Date: 03.06.2021, Decision No: 615). No written informed consent was obtained because of the retrospective design of the study. Permission for the study was obtained from Balıkesir Provincial Health Directorate and Atatürk City Hospital (E-51829602-604.01.02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Data Collection

This retrospective study was conducted in 102 term neonates who were diagnosed with HD and hospitalized to NICU of Balıkesir Atatürk City Hospital between October 2018- June 2021. Neonates with a Na level above 145 mEq/L and with a weight loss above 7% were included, patients with underlying congenital malformations, chromosomal anomalies or metabolic/neurological diseases such as hypotonia, traumatic birth, hypoxic ischemic encephalopathy, a history of diarrhea and babies with gestational weeks <37 were excluded from the study. Medical files of the neonates and their mothers were evaluated retrospectively. Information regarding the neonates' gender, gestational age (weeks), type of birth (cesarean or normal vaginal delivery), birth weight (gr); postnatal day, season and weight loss percentage on admission; feeding source (human milk/formula/mixed), laboratory findings (Na, potassium, urea, creatinine, transaminases, total and direct bilirubin, uric acid, albumin, glucose levels, complete blood count) and blood gases analyses (acidosis/alkalosis, lactate, base excess, methemoglobin and carboxyhemoglobin levels); duration of intravenous fluids and correction of hypernatremia, presence of C reactive protein (CRP) positivity and antibiotic usage, and the presenting complaint on admission to emergency department, any pathologic findings on abdomen and transfontanelle ultrasound, presence of ABO and/or Rh incompatibility and presence of early term births (i.e. gestational weeks between 37 and 38+6/7) were recorded. Degree of hypernatremia was defined as mild (145-149 mEq/L), moderate (150-159 mEq/L) and severe (≥ 160mEq/L) according to Na levels (3). The risk factors of HD, including maternal age, parity, residence (urban or suburban/rural), level of education, presence of smoking, gender and gestational age of the neonate, type of birth, and any significant effect of these factors on serum Na levels, length of NICU stay, and percentage of weight loss were recorded.

Our NICU's protocol for treating hypernatremic dehydrated neonates entails administering saline solutions with a Na concentration of 0.45–0.9% and initiating breastfeeding as soon as possible. Severely dehydrated infants receive an additional initial bolus of 15-20 ml/kg 0.9% saline.

Statistical Analysis

Data was analysed using SPSS software version 24 (SPSS Inc. Chicago, Illinois, USA) program. Categorical data were presented with n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed. Mann-

Whitney U-test was used in comparison of independent two goups. In comparison of independent four groups with non-normally distributed data, Kruskal Wallis test was used. Spearman and Pearson correlation tests were used for the correlation analysis. Statistical significance was set as $p<0.05$.

RESULTS

The rate of hospitalized infants with a diagnosis of HD was 4.2% among hospitalized newborns. The mean serum Na level was detected as 152.1±4.2 mEq/L, with the highest level being 166 mEq/L. Mild, moderate and severe hypernatremia was found in 34 (33%), 62 (61%) and 6 (6%) patients, respectively. Eighty seven patients (86%) were admitted from home, and the remaining 15 patients (14%) were admitted from the postnatal ward. The mean birth weight was 3336±461g, weight on hospital admission 2932±421g, weight loss percentage was 12±3.3%, median gestational weeks at birth was 39 (IQR 38-40) weeks, postnatal age on admission was 3.2 (IQR 3-5) days, duration of intravenous fluids 48 (IQR 24-48) hours, mean correction of hypernatremia was 36,4±17.89 hours and the average length of NICU stay was 7.2±3.2 days. Maternal demographic features are presented in **Table 1**. Laboratory findings of hypernatremic neonates are shown in detail in **Table 2**.

Table 1. Maternal demographic characteristics of neonates with hypernatremic dehydration

Gestational age (weeks)	39 (38-40)
Maternal age(yrs)	27.4 (±4.29)
Maternal level of education	
None or primary	22 (22%)
Secondary and high school	46 (45%)
University and doctorate	34 (33%)
Residence	
Urban	67 (66%)
Suburban and rural	35 (34%)
Parity	
Primiparous	75 (74%)
Multiparous	27 (26%)
Type of birth	
Vaginal delivery	55 (54%)
Cesarean section	47 (46%)
Maternal smoking	19 (18.6%)
Feeding	
Breastfeeding	92 (90%)
Formula feeding	-
Mixed	10 (10%)
Season on admission	
Winter	34 (33%)
Spring	14 (14%)
Summer	28 (27%)
Autumn	26 (26%)

Values expressed as median (interquartile range), n (%) or mean (± std).

Table 2. Laboratory findings of neonates with hypernatremic dehydration

Parameter	Mean ± standard deviation
WBC (cells/mm3)	12981±3964
Hemoglobin (g/dl)	17.35±2.37
Hematocrite (%)	50.9±6.34
Platelet count (cells/mm3)	298030±94534
Sodium (mEq/L)	152.1±4.2
Potassium (mEq/L)	4.8±0.4
Glucose (mg/dl)	60±16
Urea (mg/dl)	54.2±36.9
Creatinine (mg/dl)	0.83±0.28
AST (IU/L)	52.6±25,3
ALT (IU/L)	21±15.4
Total bilirubin (mg/dl)	13.3±5.3
Direct bilirubin (mg/dl)	0.6±0.23
Albumin (g/dl)	4.1±0.36
Uric acid (mg/dl)	6.5±2.1
pH	7.37±0.6
Lactate	3.4±1.2
Base excess	-5.9±-3.1
Methemoglobin	2.2±1.5
Carboxyhemoglobin	1.25±0.6

WBC: White blood cell count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Males and females made up an equal number of newborns, with each constituting 50% of the total. Thirty seven babies (38%) were born early term. The presenting complaint on admission was poor oral intake in 59 (58%), jaundice in 54 (53%), fever in 37 (36%), irritability in 33 (32%) and red color changes in diapers in 6 (6%) patients. Only 20% of infants tested positive for CRP, whereas 48% of infants were administered antibiotics. Ultrasonographic examination was performed in 61 (60%) neonates, nephrocalcinosis was detected in 10 (9.8%). No anomaly was detected by transfontanelle ultrasound. Cranial magnetic resonance imaging was performed in three patients with severe hypernatremia and no pathology was detected. Major blood group (ABO/Rh) incompatibility was detected in 17 (16.5%) neonates. There was no significant difference between neonates with and without major blood group incompatibility in terms of serum Na concentrations and percentages of weight loss (152.5±3.5mEq/L vs. 152.2±4.3mEq/l and 11.4±1.7% vs. 12.3±3.5%, p=0.52 and p=0.68, respectively), but postnatal day on admission was significantly lower in neonates with major blood group incompatibility (median 3 [IQR 2-3] days vs. 4 [IQR 3-5] days, p=0.003) and methemoglobin levels were significantly higher (2.2±1.5 vs. 1.2±0.25, p=0.006).

Serum Na levels significantly correlated with postnatal day on admission (r=0.433, p<0.001), weight loss percentage (r=0.522, p<0.001), duration of intravenous fluids (r=0.216, p=0.003), urea levels (r=0.380, p<0.001), creatinine levels

(r=0.220, p=0.03), albumin levels (r=0.317, p=0.002) and living in rural/suburban areas (r=0.320, p=0.001). There was a significant correlation between percentages of weight loss and thrombocyte levels (r=0.297, p=0.03) and a significant inverse correlation between weight loss percentages and pH levels of blood gases (r=-0.270, p=0.03). Neonates of mothers living in rural/suburban communities had significantly higher serum Na levels (**Table 3**). No significant correlation was found between weight loss percentage and birth type, gender, gestational age, or occupation (**Table 3**). There was no correlation between maternal age and serum Na levels, percentage of weight loss, postnatal day on admission, or length of NICU stay (r=0.044, p=0.67; r=-0.530, p=0.61; r=-0.155, p=0.13; r=0.170, p=0.10, respectively).

Cesarean-delivered infants exhibited greater weight loss (12.83.0% vs. 11.63.5%, p=0.01), were born to mothers with a higher level of education (88.6% non-primary vs. 68.1% mid-high graduate, p=0.02), and had higher bilirubin levels (14.2±5.2 mg/dl vs. 11.2±5.2 mg/dl, p=0.04). The serum Na levels, postnatal day on admission, and hematocrit levels (52.1±6.2% vs. 50.1±6.3%, p=0.04) of rural and suburban newborns were significantly higher than those of urban newborns (**Table 3**). There was no significant difference between maternal education levels and serum Na levels, percentage of weight loss, postnatal day at admission, or length of NICU stay (**Table 3**). In babies born to mothers who smoked, the rate of weight loss was statistically significantly higher and serum sodium levels were higher but not statistically significant (**Table 3**). Blood gas analyses, including carbon monoxide and methemoglobin levels, revealed no significant differences between babies born to smoking vs. non-smoking mothers (1.18±0.64 vs. 1.26±0.63 and 2.0±0.73 vs. 2.0±1.50, p=0.54 and p=0.67, respectively). There was no significant difference in serum Na levels, postnatal day on admission, between primiparous and multiparous mothers. Comparing the percentages of weight loss and length of NICU stays for primiparous and multiparous mothers is presented in **Table 3**.

Early term infants were found to have lower Na levels (151.1±3.4 mEq/L vs. 153.4±4.5 mEq/L, p=0.01), higher methemoglobin levels on blood gases (2.4±2.0 vs. 1.6±0.6, p=0.02), lower blood glucose levels (53±15 mg/dl vs. 64±16 mg/dl, p=0.002), higher antibiotic usage rates (61% vs. 41%, p=0.04) and fed with mixed diet (4/37 vs. 6/65, p=0.04). There were no statistically significant gender differences in percentage of weight loss, postnatal day on admission, or length of NICU stay; however, creatinine was significantly higher in males (0.76±0.28 mg/dl vs. 0.89±0.28 mg/dl, p=0.005 and **Table 3**).

DISCUSSION

American Academy of Pediatrics recommends neonates with weight loss exceeding 7% of their weights evaluated promptly for medical history, physical examination of baby and mothers' breast, observation of breastfeeding and laboratory findings if necessary (15). The exact incidence of neonatal HD is difficult to evaluate due to differences in geographical location, limited availability of hospital and postdischarge data (6). Incidence of

Table 3. The effect of maternal-neonatal risk factors on serum Na levels, weight loss percentages, postnatal day on admission and length of NICU stay.

	Serum Na level mEq/L	Weight loss percentage %	Postnatal day on admission (day)	Length of NICU stay (day)
Parity				
Primiparous	152.2±4.2	12.2±3.3	4 (3-5)	7 (5-8)
Multiparous	152.5±4.0	12.3±3.5	4 (3-5)	7 (5-8)
Type of birth				
Cesarean section	152.1±4.4	12.8±3.0[a]	3.5 (3-5)	6 (5-8)
Vaginal delivery	152.3±4.0	11.6±3.5[a]	4 (3-5)	7 (5-9)
Gender				
Female	152.4±4.0	12.5±3.3	3 (3-5)	7 (5-8)
Male	152.0±4.1	11.9±3.2	4 (3-5)	7 (5-8)
Maternal level of education				
None or primary	152.7±4.8	11.9±37	4 (3-5)	6 (4-7)
Secondary/high school	152.5±5.1	12.8±3.8	4 (3-5)	7 (7-8)
University/doctorate	151.7±2.3	11.8±2.3	3.75 (3-4.25)	7 (5-8)
Maternal smoking				
Yes	154.6±5.8[b]	14.3±3.8[c]	4 (3-5)	7 (5-8)
No	151.7±3.6[b]	11.7±3.1[c]	4 (3-5)	7 (5-9)
Occupation				
Rural/suburban	153.9±4.8[d]	12.9±3.8	4.5 (4-6)[e]	7 (5-8)
Urban	151.2±3.4[d]	11.7±2.9	3 (3-4)[e]	7 (5-9)

Values expressed as median (interquartile range) or mean (± std), [a]Comparison of two yielded a p-value=0.01, [b]Comparison of two yielded a p-value=0.05, [c]Comparison of two yielded a p-value=0.003, [d]Comparison of two yielded a p-value=0.008, [e]Comparison of two yielded a p-value=0.02

neonatal HD in postdischarge neonates may range between 1% to 5.6% (16, 17). A retrospective study including 3718 neonates within 28 days of life hospitalized to a tertiary care center between 1997 and 2001 reported incidence of breastfeeding-associated hypernatremic hypovolemia as 1.9 percent (18). Another retrospective study from a different region of our country reported the frequency of HD in all live, healthy term births and in all hospitalized children as 0.7 and 3.1, respectively (19). The rate of hospitalized infants with the diagnosis of HD was 4.2% of all hospitalized newborns. Our study, similar to majority of literature, gives data of hospitalized children. The true incidence of HD in all live births could not be determined because there is no screening for hypernatremia in the first week of life and not all babies born in our hospital present to our hospital for control visits and/or hospitalization. Therefore the true incidence of HD could be much more than reported due to missing and undiagnosed cases.

Approximately 15% of exclusively breastfed infants exhibit excessive weight loss (>10% of birth weight), resulting in hypernatremia in a third of these infants (20). Multiple studies have demonstrated that approximately 95% to 98% of hypernatremia occurs in exclusively or near-exclusively breastfed infants (21, 22), similar to the findings of the present study in which 92% of infants were exclusively breastfed and only 8% were fed a mixed diet. Bhat et al. (23) also reported that exclusively breastfed neonates could lose more than 10% of their weight per day with a frequency of 6.8% and less than 5% per day with a frequency of 24.7%, respectively. In contrast, the study conducted by Gonzalez et al. (5) found comparable rates of HD in neonates who were exclusively breastfed or mixed-fed.

Multiple studies to date have sought to determine the risk factors for developing hypernatremia. Maternal social and biological risk factors may be involved in lactation and breastfeeding interference, thereby contributing to the development of HD. Age, level of education, and experience with child care can affect the intervention of caregivers (mothers). Primiparity has been cited in the majority of studies as one of the most significant risk factors for the development of HD, reflecting the lack of experience and failure to recognize the symptoms and severity of dehydration (14,20,24). Surprisingly, another study identified multiparity as a risk factor for HD, in contrast to the literature which suggests that primiparity causes delayed and inadequate lactogenesis. The investigators concluded that primiparous mothers were monitored more closely during the first postnatal days (4). In our study, the vast majority of mothers (74%) were primiparous, indicating likely less experience with breastfeeding and recognizing the signs of dehydration. However, there was no correlation between parity and serum Na levels, degree of dehydration, or postnatal day at admission; but bilirubin levels were statistically greater in primiparous mothers.

Regarding the association between the mother's level of education and HD, contradictory results have been reported in the literature. Some studies demonstrated that mothers of dehydrated newborns have a low level of education (25-27). On the other hand, Gonzalez et al. (5). demonstrated that having a mother with a higher level of education increases the risk of hypernatremia, which may be explained by the increased willingness of highly educated mothers to breastfeed exclusively. Several studies have found no correlation between maternal education and the degree of dehydration of their offspring (28, 29). Maternal age has also been considered a significant factor in dehydration and hypernatremia (30). In our study, we did not find any correlation between maternal age, education level, serum Na levels, and weight loss percentages.

Due to the inability to breastfeed, cesarean section has been regarded as a significant risk factor for HD in newborns (4,30). Evans et al. (31) found that during the first six days of life, infants born via cesarean delivery received less milk than those born vaginally. Nonetheless, a number of studies found no correlation between type of delivery and serum Na levels and dehydration (14,28). In our study, babies born via cesarean section had greater weight loss than those born vaginally, but there was no difference in Na levels. Data favoring males for the development of HD predominate in the scientific literature (4,14,26). This difference has been attributed to organ immaturity and greater oxidative stress in male infants by Diaz Castro et al. (32). In our study, we found no difference between males and females in terms of Na levels, percentages of weight loss, or laboratory findings, with the exception of males' statistically higher creatinine levels, which most likely indicated a greater muscle mass.

Akgün et al. (25) reported that HD is more prevalent in warm seasons, whereas another study found that the incidence of significant weight loss, clinical dehydration, hypernatremia, and hyperbilirubinemia was higher in the warm months, but the difference was not statistically significant (23). In contrast, Uras et al. (17) determined that season is not a risk factor for the development of HD. In contrast to the majority of literature, the majority of patients in this study were admitted during cold seasons, and we did not find a correlation between serum levels, dehydration severity, and seasons. There are few data regarding the association between neonatal HD and residence (urban/rural). In our study, neonates whose mothers lived in rural and suburban areas had higher serum Na and hematocrit levels and were admitted

to the emergency department later than those whose mothers lived in urban areas, likely indicating a delay in care-seeking for infants with signs and symptoms of dehydration.

Clinical manifestations of HD may include jaundice, fever, poor oral intake, decreased urinary output, irritability, and lethargy; however, these symptoms are nonspecific and may be indicative of a variety of diseases in neonates (12). Being a sleepy, quiet infant can delay the diagnosis of HD. As a result of fluid shift from intracellular to extracellular areas, clinical findings can be sparse and may be more noticeable in the advanced stages of dehydration. In a study involving 159 newborns, fever and jaundice were the most prevalent symptoms upon admission (19). In the study by Akdeniz et al. (33), decreased sucking was the most prevalent symptom. In our study, poor oral intake (58%) was the most prevalent symptom, followed by jaundice (53%) and fever (36%). In the present study, platelet levels were positively correlated with weight loss percentages, while pH levels of blood gases analyses were negatively correlated. However, there was no correlation between thrombocyte levels and serum Na levels. On the other hand, Boskabadi et al. (34) have demonstrated a strong correlation between hypernatremia and thrombocytopenia and a poorer prognosis and significantly more complications in thrombocytopenia patients. Babies born early term were found to have significantly lower serum sodium and glucose levels, higher antimicrobial usage rates, and a higher frequency of mixed feeding. These results could be explained by their low birth weights and feeding difficulties compared to more mature term infants, and the likelihood that their families brought them to the hospital sooner.

In pediatric patients, diarrhea and sepsis are known to cause acquired methemoglobinemia (35). In our study, the methemoglobin levels of CRP-positive patients did not differ from those of CRP-negative patients, but there was a correlation with hospitalization day and weight loss percentages, which may reflect the degree of dehydration, however, there was no correlation between methemoglobin and sodium levels. Maternal exposure to tobacco smoke in pregnancy has been linked to preterm birth, neonatal mortality, fetal growth retardation and sudden infant death syndrome (36), but there are no data about the relationship between maternal smoking and neonatal HD. Present study founded significantly higher percentages of weight loss and non-significant higher serum Na levels in neonates of smoking mothers, but there was no significant difference between carbonmonoxide levels in neonates of smoking and non smoking mothers. Our findings regarding the effects of maternal smoking on neonatal dehydration and hypernatremia are comparable to those of Mennella et al. (37), who found that smoking mothers were less likely to breastfeed and that smoking could have dose-dependent negative effects on lactation.

This study has some limitations. Although the clinical significance of elevated breast milk Na levels is not well explained, they have been linked to lactation failure (38). The inability to test breast milk samples for sodium levels is one of the limitations of the current study. And the study demonstrates the results of hospitalized neonates, probably representing the visible part of the iceberg, because there is no hypernatremia screening policy. Nearly half of infants with hypernatremia >150 mEq/L have abnormal developmental scores at 12 months of age, while 21% of infants have developmental delay at 12 months, 19% at 18 months, and 12% at 24 months (39, 40). Unfortunately, we have no information about the long-term neurological development of HD infants in their most crucial first three years of life.

CONCLUSION

Hypernatremic dehydration, despite its life-threatening complications, is a preventable and treatable disease of previously healthy infants. During the first two to four days, it is vital to assess the infant and observe breastfeeding and mother-infant feeding interaction. Important in the development of dehydration and HD are maternal social-biological and neonatal risk factors such as residence (rural/suburban living), maternal smoking, being an early term baby, and being born via cesarean section. Proper education and sensitization of mothers regarding the signs of dehydration, recognition of problems associated with breast-feeding, and maintenance of early control visits in the 2-4 days after early discharges, before dehydration occurs, are crucial for the identification of potential cases carrying risk factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medipol University Non-Interventional Researches Ethics Committee (Date: 03.06.2021, Decision No: 615).

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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Factors associated with challenges in skin wound length and depth prediction of physicians in forensic cases

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ABSTRACT

Aim: We aimed to display factors associated with error rates in identifying skin lesions with subjective methods and determine potential effectiveness of objective and metric measurements on judicial processes which may result in unwanted social and legal outcomes and raise the awareness of physicians.

Material and Method: We made an incision on a piece of sponge with a lencet in order to model a skin lesion. The length and depth of the lesion was measured by compass device. Then, a face to face interview was planned with the physicians working in the hospital and they were asked to estimate the length and depth of the lesion. Estimations of the physicians were recorded.

Results: Total of 146 physicians were involved into the study. Of these, 41.8% (n=61) were female and 58.2% (n=85) were male. Mean age of the physicians was 33.46±7.94 (24-61) years. Of the physicians, 7.5% (n=11) were a member of basic medical sciences, 26% (n=38) were a member of surgical medical sciences and 21.9% (n=32) were practitioner physician. When titles of the physicians were investigated, it was found that 21.9% (n=32) were practitioners, 34.9% (n=51) were residents, 34.9% (n=51) were specialists, 8.2% (n=12) were lecturers. The rate of the participants who estimated the incision more than 8 cm was higher than those who estimated less than 8 cm. Standart deviation of the depth estimation was 1.35 cm. Thirty-nine (26.7%) participants made an exact estimation of the depth of the incision.

Conclusion: The measurement accuracy without a device is not associated with experience and errors of both inexperienced physicians and experienced physicians of any grade do similar mistakes during judicial report preparation process. These high error levels reveal that use of devices may avoid errors of physicians at any grade and protect physicians from possible judicial challenges.

Keywords: Forensic, skin lesions, measurement

INTRODUCTION

Any damage caused by a physical or chemical agent on the skin, all other tissues and internal organs is considered as "wound". The wounds need to be described with a full disclosure during or shortly after the examination. This description is to help determine how the injury occurred later in the legal process. If the wounds are not defined correctly, a process that puts the clinician in a difficult situation will occur (1). It is the responsibility of all physicians to report patients and their lesions to judicial authorities. This responsibility of physicians comes from their expert and wittness titles (2-6). It is a known fact that physicians have some difficulties in forensic report process (2). However physicians may not be aware of their responsibility as required or have enough experience due to negligence during and post-medical education period (3). Hence, it is inevitable to make mistakes and deficiencies in forensic reports and face juidicial processes.

Accuracy rate in defining penetrating and visible wounds affects all juidical processes in terms of National Penal Laws. When preparing a forensic report, wound must be defined correctly; depth, width and length of the wound must be measured and registered correctly (7).

Determining the extent of a wound is perhaps the easiest step in wound identification. However, measurement of wound dimensions is the most frequently neglected detection method in medical records. The measurement of wound dimensions should be determined using a ruler or caliper and recorded in centimeters or millimeters. The concept of depth is important for some wounds, but it is often not possible to determine this in living persons (1).

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In this study, we aimed to display factors associated with error rates in identifying skin lesions with subjective methods. We also aimed to determine potential effectiveness of objective and metric measurements on judicial processes which may result in unwanted social and legal outcomes and raise the awareness of physicians.

MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Non-interventional Researches Ethics Committee (Date: 31.05.2022, Decision No: 2022-13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted with face to face interviews with physicians actively working in Hitit University Training and Research Hospital between 01.07.2022 and 01.10.2022. We made an incision on a piece of sponge (30 cm of length, 30 cm width, 5 cm depth) with a lencet in order to model a skin lesion (**Figure 1**). The length and depth of the lesion was measured by compass device. Then, a face to face interview was planned with the physicians working in the hospital and they were asked to estimate the length and depth of the lesion as if they were writing a forensic report. The physicians were allowed to evaluate the lesion by palpation. Length and depth estimations of the physicians were recorded. Estimations showing full agreement with the compass device measurements were accepted as correct. All other estimations were considered estimation errors. Also; demographical characteristics of the physicians (age, gender, speciality), titles and whether they actively edit forensic reports or not were recorded. Lately, metric measurements by compass device were compared with the palpational measurements of the physicians.

Compass device: A compass device is used for accurate measurement. With it, an accurate measurement of length, width, depth, internal and external diameter measurements can be performed. It has digital and mechanical types. In our study a device which has a sensitivity of 0.1 mm was used (Trademark: Piranha, Digital Compass, Model: PDC1850) (**Figure 2**).

Statistical Analysis

Data were statistically analyzed using the SPSS package program (Version 22, SPSS Inc., Chicago, IL, USA). For categorical variables, number (n) and percentage (%) were used in reporting data. Descriptive statistics of numerical variables collected through measurement were reported using the mean±standard deviation or median (min-max), depending on the distribution of the data. The normal distribution of data checked using the Shapiro-Wilk test. The Mann Whitney U test was used to compare non-normally distributed data between two independent groups. The Kruskal-Wallis test was used to compare non-normally distributed data between more than two independent groups. Statistical significance level was accepted as $p<0.05$ in all comparisons.

Figure 1. Incision on a piece of sponge with a lencet in order to model a skin lesion

Figure 2. The compass device that is used for accurate measurement

Table 1. Comparison of estimation errors of incision length and depth among sociodemographic characteristics (n=146)

	n	Estimation errors of incision length	P	Estimation errors of incision depth	P
Gender			0.090[a]		0.822[a]
Male	85	1.5 (0-7) (1.71±1.44)		1 (0-4) (0.96±0.89)	
Female	61	2 (0-12) (2.55±2.57)		1 (0-8) (1.29±1.59)	
Speciality			0.535[b]		0.579[b]
Basic Medical Sciences	11	1 (0-5) (1.68±1.55)		0.5 (0-3) (0.86±0.92)	
Surgical Medical Sciences	38	2 (0-7) (1.97±1.77)		1 (0-4) (1.17±1.07)	
Internal Medical Sciences	65	2 (0-12) (2.42±2.5)		0.5 (0-8) (1.23±1.51)	
General Practitioner	32	1 (0-5) (1.59±1.13)		1 (0-3) (0.82±0.82)	
Degree			0.160[b]		0.637[b]
General Practitioner	32	1 (0-5) (1.59±1.13)		1 (0-3) (0.82±0.82)	
Assistant Doctor	51	2 (0-12) (2.17±2.08)		0.5 (0-6) (1.16±1.31)	
Specialist Doctor	51	2 (0-12) (2.41±2.37)		1 (0-8) (1.18±1.43)	
Faculty Member / Academician	12	1 (0-7) (1.41±1.91)		1 (0-3) (1.20±0.96)	
Department			0.517[a]		0.601[a]
Clinic	135	2 (0-12) (2.1±2.06)		1 (0-8) (1.12±1.26)	
Basic Medical Sciences	11	1 (0-5) (1.68±1.55)		0.5 (0-3) (0.86±0.92)	
Do physicians actively write forensic reports?			0.681[a]		0.591[a]
Physicians writing	92	2 (0-7) (1.97±1.75)		1 (0-6) (1.03±1.10)	
Physicians not writing	54	2 (0-12) (2.23±2.43)		1 (0-8) (1.22±1.44)	

[a]Mann-Whitney test with median (min-max) (mean±standard deviation), [b]Kruskal-Wallis test with median (min-max) (mean±standard deviation)

RESULTS

Total of 146 physicians were involved into the study. Of these, 41.8% (n=61) were female and 58.2% (n=85) were male. Mean age of the physicians was 33.46±7.94 (24-61) years. While 92.5% (n=135) were active in the clinics, 7.5% (n=11) were involved in basic sciences. Of the physicians, 63% (n=92) were actively editing forensic reports, 37% (n=54) were not.

Table 1 represents the comparison of estimation errors with socio-demographical characteristics. Any statistical significance could not be determined in terms of gender, branches, title, department, actively editing forensic reports and prediction of length and depth of the incisions (P>0.05).

In **Table 2**, correlation between estimation errors on length and depth estimations and age-occupational experience are represented. There was not any statistical significance between length and depth estimation errors of the lesion and age and occupational experience of the participants (P>0.05).

Table 2. Correlation analysis results between the length and depth estimation errors of the incision, and age and professional experience (n =146)

		Age	Vocational experience (year)
Estimation errors of incision length	r	-0.015	-0.009
	p	0.856	0.917
Estimation errors of incision depth	r	-0.020	0.007
	p	0.808	0.929

Spearman correlation coefficient

Standart deviation of the length was 2.61 cm. Twenty participants (13.7%) could make the exact estimation. Length estimation varied between 6 and 10 cm. The rate of the participants who estimated the incision more than 8 cm was higher than those who estimated less than 8 cm.

Standart deviation of the depth estimation was 1.35 cm. Thirty-nine (26.7%) participants made an exact estimation of the depth of the incision.

Figure 3 represents box plots of the distribution of estimation errors of depth and lenght according to different properties and status; **Figure 4** represents Scatter plots showing the errors between the estimated length-depth and the actual length-depth without using a measuring instrument and **Figure 5** represents Scatterplots showing the relationship between length-depth estimated error values and diffefent properties.

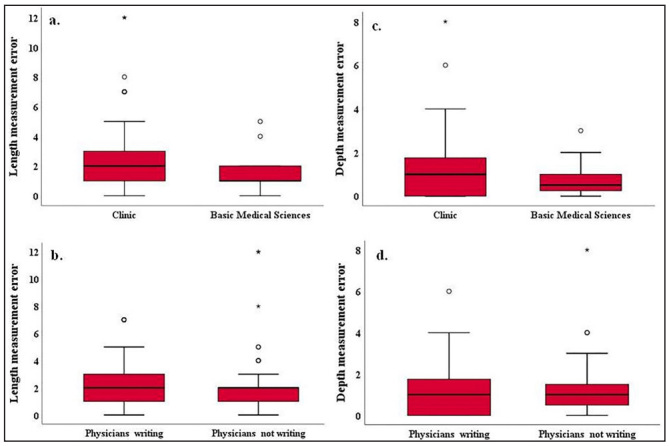

Figure 3.
a. Box plot of the distribution of estimation errors of length according to clinic or basic medical sciences groups
b. Box plot of the distribution of estimation errors of length according to their active forensic report writing status
c. Box plot of the distribution of estimation errors of depth according to clinic or basic medical sciences groups
d. Box plot of the distribution of estimation errors of depth according to their active forensic report writing status

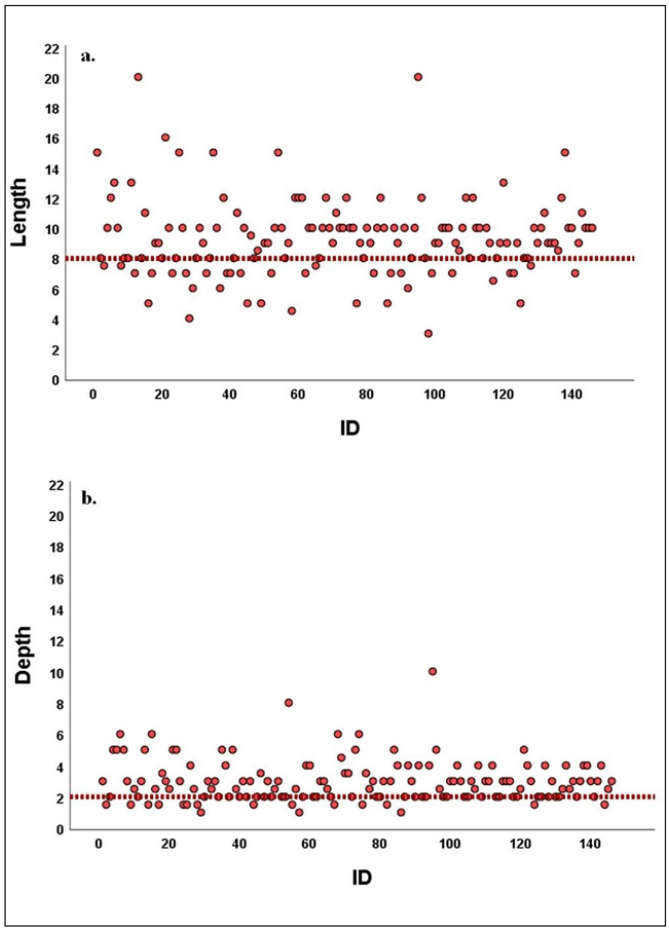

Figure 4.
a. Scatter plot showing the errors between the estimated length and the actual length without using a measuring instrument
b. Scatter plot showing the errors between the estimated depth and the actual depth without using a measuring instrument

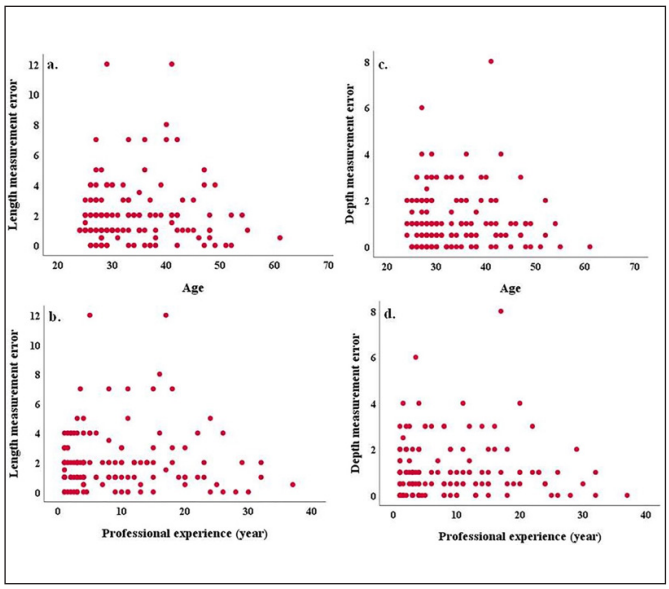

Figure 5.
a. Scatterplot showing the relationship between length estimation errors values and age
b. Scatterplot showing the relationship between length estimation errors values and professional experience (year)
c. Scatterplot showing the relationship between depth estimation errors values and age
d. Scatterplot showing the relationship between depth estimation errors values and professional experience (year)

DISCUSSION

Physicians have the responsibility to recognize forensic cases and report these cases to judicial authorities besides responsibility to examine and treat the patient. In Turkey, there is a seperate law (Turkish Penal Code Number 5237, item 280) for healthcare providers (8).

Physicians must prepare a forensic report about severity level of lesion (11). These reports are essential for criminal and civil cases and they must meet the requirements in Turkish Penal Code. In every forensic case, "life threatening" condition must be sought and length, width and depth of all the wounds must be written in details (12,13).

Emergency departments are of greater importance since first examination of forensic cases are performed in these settings. The physicians in the ED are the only ones who observe the wound before and after the treatment. The characteristics of the wound must be reported correctly. It must be kept in mind that the characteristics of the wound may alter following treatment. Methods of wound description should be chosen carefully. Nevertheless, a universal method for wound description has not been developed so far (14). Techniques for measurement vary from simple to complex. The most common method is measurement by a ruler (15). In order to avoid infections, use of disposable rulers are recommended.

It is suggested that all wound measurements should be recorded as length (L), width (W) and depth (D) in centimeters. A standardized system is required for wound description. This is essential for avoiding inconsistencies in reports. It must be assured that the incision is measured in maximum diameter to determine the exact size. The ruler must be placed in the maximum width of the wound. The diameter of the wound must be determined if the wound is round If the wound is round, the widest part is measured as diameter. For depth measurement, a cotton bud may be used. The cotton bud may gently be placed into the deepest part of the wound and the depth of the wound is measured. A brief description of the wound must be recorded (rough, smooth, puffy or flowing) (16).

Studies have shown that the most common error in wound description is made in wound borders (17). It must be kept in mind that palpations and manupilations during examination may alter the morphology and size of the wound. Even gentle interventions may change the appearance of the wound and size of a wound on a curved part of the body (such as heel) is difficult to measure. Additionally a wound may be highly damaged and measurement of its volume may be challenging (14). We aimed to investigate factors associated with

observational incision measurement of wound length and depth without use of any device, which is performed by many physicians in Turkey, and propose an accurate method of measurement to be helpful to constitute an equitable judicial process.

For the participants; there was not any statistical significance between gender, speciality, department, and forensic report preparation and errors in length and depth estimations of the wound. Accordingly, there was not any relationship between age and experience, and length and depth estimation of the physician. These results reveal that measurement accuracy without a device is not associated with experience and errors of both inexperienced physicians and experienced physicians of any grade do similar mistakes during forensic report preparation process.

In the literature, errors in patient identity, timing of the event, signature of the physician, consciousness level of the patient, systemic examination findings, threathening of life, and alcohol level are well-defined (3, 18). In a study involving forensic reports of 2478 patients, it was revealed that external wounds were not reported in details in 46.1%, threathening of life was not stated in 7.6%, and whether the injury required simple medical intervention or not was not recorded in 8.9% by Emergency Medicine residents (18). Whereas, physicians should report if the injury required simple medical intervention according to "Forensic Evaluation Guide of Injury Crimes" defined in Turkish Penal Code. According to this guide, single lesion <5 cm on scalp or face with a total of 10 cm and cutaneous or subcutaneous lesions with a total of <20 cm are defined as simple lesions requiring simple medical intervention. Lesions larger than above-metioned ones are defined as complex wounds requiring more than simple medical intervention (19). In our study, the rate of correct estimation of wound length and depth was 13.7% and 26.7%, respectively. These low correct estimation levels reveal that use of devices may avoid errors of physicians at any grade, help settling justice in judicial processes and protect physicians from possible judicial challenges.

One study demonstrated high interobserver variability and inaccuracy in wound size estimation. It has been reported that this condition is related to gender. Generally, it has been reported that male doctors are more likely to overestimate the size of wounds, while their female colleagues are more likely to underestimate the size. In the description of traumatic wounds, it has been suggested to measure accurately using ruler measurement (20). In our study, no difference was observed between the genders, but the rate of accurate estimation of wound size was found low.

In another study on forensic reports, it was shown that external wounds were not described in 30.5% of the patients and in almost half of them, external wounds were not described properly in details in forensic reports. (3). In the study, besides, it was shown that in approximately 1/3 of the patients, lesions were not marked on the body diagram in the forensic report. (21). Our study is of importance since it reveals the importance of recording forensic wounds accurately. However, studies in the literature state that it is also important to record lesions accurately as well as accurate measurements. There is a lack of information on their judicial and medical responsibilities about forensic reports among physicians in Turkey (8, 22). This study may contribute to awareness of physicians about forensic report preparation.

In future studies; inaccuracies in the description of wounds in different body parts and their effects on judicial processes should be examined. For this purpose, quantitative identification methods should be proposed for each body region and for each injury pattern. In this way, it should be demonstrated with larger cohort studies that the legal problems that may be caused by subjective decisions can be avoided.

CONCLUSION

The measurement accuracy without a device is not associated with experience and errors of both inexperienced physicians and experienced physicians of any grade do similar mistakes during judicial report preparation process. These high error levels reveal that use of devices may avoid errors of physicians at any grade and protect physicians from possible judicial challenges.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Non-interventional Researches Ethics Committee (Date: 31.05.2022, Decision No: 2022-13).

Informed Consent: All participants 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 evaluation of anxiety and depression in spontaneous pneumothorax

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ABSTRACT

Aim: Psychiatric disorders are common in patients with advanced respiratory diseases. The prevalence of primary spontaneous pneumothorax ranges from 1.2-37 per 100,000 population per year, and the risk of recurrence causes anxiety and depression for the patients.

Material and Method: The Hospital Anxiety and Depression (HAD) scale was applied to 50 patients with a primary spontaneous pneumothorax that underwent treatment in our clinic and a control group of 50 individuals. The study and control group had similar participants (50 patients, 9 women and 41 men). The control group comprised otherways healthy participans aged between 18-40 who had admitted to the smoking cessation clinic.

Results: While the study group's mean age was 25.2, it was 29 in the control group (covariance analysis used for the correction). On anxiety scale, the study group's mean score was calculated as 8.6, while it was 5.7 in the control group. The difference was found to be significantly higher in the patient group. The depression scale score of the study group was 5.8, and the control group's score was 5.7. There was no statistically significant difference between the groups.

Conclusion: Since pneumothorax is a sudden, recurring, and severe illness that can cause respiratory distress, it may lead to anxiety or depression in patients. Without treatment, life-threatening consequences such as dyspnea and cardiac collapse may occur. Furthermore, the painful procedure of tube thoracostomy increases the patients' anxiety. Our objective is to identify potential anxiety-depression in pneumothorax patients, leading to improved mental health outcomes, increased satisfaction, lower readmission rates, and reduced care costs.

Keywords: Primary spontaneous pneumothorax, anxiety, depression

INTRODUCTION

Pneumothorax is the presence of air in the pleural space (1). A primary spontaneous pneumothorax (PSP) occurs without underlying lung disease or trauma. The prevalence of PSP in the general population is 7.4 per 100,000 in men and 1.2 per 100,000 in women (1). It is typically seen in tall, thin, and smoking men. Bulla and bleb structures commonly located in the lung apex are held responsible for the etiology. It is thought that cigarette smoke is involved in pathology due to the destruction of elastic fibers by disrupting the protease-antiprotease and oxidase-antioxidase balance, causing inflammation in the distal airways. PSP recurrence rates are generally cited as between 16- 52%, making counseling about forthcoming risks complex and creating uncertainty regarding optimal management. If recurrence rates are as high as 50%, a statement could be made for definitive surgical repair at an earlier stage. However, if the actual rate is closer to the lower estimate, waiting for a recurrent episode before considering surgery is appropriate (2). Unfortunately, no established factors predict recurrence and, consequently, no method for risk-stratifying patients. Female sex, lower body weight, smoking and height in males have all been proposed as risk factors for recurrence.

PSP treatment is applied in different ways depending on the clinic and the degree of pneumothorax. These can be listed as simple to invasive; observation, simple needle aspiration, percutaneous drainage catheter, tube thoracostomy, and surgical treatment. In our clinic, we don't prefer simple needle aspiration, and we perform surgical operation to patients with recurrent pneumothorax. Video-assisted thoracic surgery (VATS) is used in surgical treatment. Patients are called for outpatient clinic control on the 10th day after discharge.

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We observed increased clinic admissions with these patients, disrupting their daily work due to the disease's anxiety of recurrence. Only a few published studies have documented psychopathological abnormalities and decreased quality of life in patients with PSP (3). The study aimed to investigate whether the levels of anxiety and depression in PSP patients are higher than in the general population.

MATERIAL AND METHOD

The study was carried out with permission of University of Health Sciences Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 22.02.2023, Decision No: 2012-KAEK-15/2658). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

We obtained data on 100 young individuals from this cross-sectional survey between January 2019 and January 2020. The control group (n=50) comprised individuals admitted to the smoking cessation clinic. To ensure that the volunteers had no medical history of respiratory, psychiatric, or chronic diseases, a physician conducted interviews with them. The PSP group (n=50) consisted of patients with PSP confirmed by chest radiographs or computed tomography and treated in the hospital. The HAD results of both groups were compared. All participants were between 18-40 years old and provided informed consent. The study excluded participants with known psychiatric disorders, medical therapy users, and individuals with co-existing pulmonary pathologies.

The Hospital Anxiety and Depression (HAD) scale was used to collect it in the study (**Figure 1**). HAD is a study measuring anxiety and depression in a hospital that Zigmond and Snaith described in 1983. HAD is a test that can be completed in 2-5 minutes and is easily applied in the general population. Scores below 8 are classified as non-cases, while scores between 8 and 10 indicate mild effects, and scores above 11 are positive. The hospital and non-hospital reliability of the HAD scale and the Turkish form of the scale have been proved by various studies (7,8).

Uni- and multivariate statistical analyses were done using IBM SPSS Standart Concurrent User

Version 26 (IBM Corp., Armonk, New York, USA). Spearman's rank correlation is used to analyze data. The analysis of covariance was used to adjust or control for differences between the study and control groups.

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Figure 1. Summary of assessment scores for videos regarding robotic-assisted knee replacement videos

RESULTS

The study included 50 patients with primary spontaneous pneumothorax (9 women, 41 men) and 50 healthy controls (11 women, 39 men). The control population comprises individuals who have applied to the smoking cessation clinic with a mean age of 29.8 and no history of illness. The mean age of the patient group was 25.2 (18-40) compared to 29.8 (18-40) in the control group, covariance analysis is used for correction.

The mean number of hospital admission was 8.9 (2-39), and the number of hospitalization was 1.9 (1-6). The mean hospitalization rate after admission to the hospital was %26.3 (7.7-66.7%). The patient group had a higher mean anxiety scale score of 8.6 when compared to the control group's mean score of 5.7. The anxiety score of the patient group was found to be significantly higher in the calculation shown by correcting the values for age ($p < 0.05$). The patient group had a depression scale score of 5.8, similar to the control group's score of 5.7.

When evaluated with Spearman's rank correlation test, the hospital admission frequency was significantly higher in patients with increased anxiety scores (p:0.12). However, there was no significant difference in

the number of hospitalization and length of stay with anxiety scores. Also, there was no significant difference between depression scores with the hospital admission frequency, the number of hospitalizations and the length of stay (**Table 1**).

Table 1. Correlation between anxiety and depression and hospital administrations and stays.

Spearman's rho	Anxiety	Depression
The hospital administration		
Correlation Coefficient	.354*	-.012
Sig. (2-tailed)	.012	.936
N	50	50
The number of hospitalizations		
Correlation Coefficient	.014	-.103
Sig. (2-tailed)	.923	.476
N	50	50
The length of stay		
Correlation Coefficient	.150	-.053
Sig. (2-tailed)	.297	.716
N	50	50

*Correlation is significant at the 0.05 level (2-tailed)

Twenty-six of the cases had a recurrence of PSP (52%). Surgery (VATS Bullae resection) was performed in 19 (38%) cases. 28 F chest tube was used for 45 (90%) patients, a 24 F chest tube for 3 (6%) patients and a 10 F catheter was inserted in 2 (4%) patients (**Table 2**).

Table 2. The treatment course of the patients with PSP.

	Frequency	Percent
10 F Pleurocan	2	4.0
24 F Chest TUBE	3	6.0
Recurrence	26	52.0
Surgery	19	38.0

DISCUSSION

In this study, we found that the prevalence of anxiety in PSP was significantly higher than in the control group. The frequency of admission to the hospital was also found to be significantly increased in patients with anxiety. Pneumothorax is an annoying disorder that presents with a variable spectrum. It may occur in young and healthy patients without a precipitating external event and the absence of clinical lung disease (PSP) or as an underlying lung disorder complication (secondary pneumothorax).

A few methods have been described to evaluate pneumothorax size. The light index calculates pneumothorax dimensions from the ratio of cubed diameters of collapsed lung and hemithorax on a chest radiograph (pneumothorax size [%] = 100 × [1 – average lung diameter3/average hemithorax diameter3]) and demonstrates a good correlation with the volume of air removed (4). Jalli et al. (5) prospectively compared the precision of ultrasound with chest radiography in the detection of pneumothorax, using a CT scan as the reference standard. The sensitivity and specificity in the detection of PSP were 80.4% and 89%, respectively, with an overall accuracy of 85%.

Moreover, the treatment options are also variable. Observation, needle aspiration, and chest tube insertion are generally recommended for the first episode of pneumothorax.

Concerning the interventional treatment, the indication to drain the air magnitude from the pleural space can be conducted using aspiration or a chest tube. A permanent catheter is more often suggested rather than simple aspiration (6, 7). Bullae resection with VATS have excellent results in terms of low rate of recurrence after surgery, length of hospital stay, functional recovery and cosmetic outcomes when compared to thoracotomy (8-11).

For recurrent or persistent pneumothorax, chemical pleurodesis, surgery by video-assisted thoracic surgery (VATS) or thoracotomy may be helpful (12).

Although PSP is not associated with a known clinical lung disease (e.g., COPD), most of the affected patients have unrecognized lung abnormalities (mostly sub-pleural blebs) that likely predispose to pneumothorax (13).

Anxiety disorders and depressive disorders are approvingly prevalent conditions that frequently co-occur. Individuals impacted by anxiety and depressive disorders concurrently have commonly shown more significant functioning impairment, decreased quality of life, and inferior treatment outcomes than individuals with only one disorder (14). Rare reports have demonstrated psychopathological anomalies in patients with pneumothorax (3,13,18). A study evaluated the etiology of primary spontaneous pneumothorax and suggested an association between anger and primary spontaneous pneumothorax (13). Other studies also examined psychological aspects, including depression, anxiety, and anger, in patients with pneumothorax compared with normal individuals; however, the result is inconsistent (3, 17).

In the study, the relationship between anxiety and depression disorders with PSP structures was evaluated. There is only a few studies on this subject in the literature (3,12,18,19).

Many studies showed that patients with advanced COPD and severe asthma is at elevated risk of recurring hospitalization and emergency care utilization episodes. These patients experience distressing symptoms of depression, anxiety, and dependence on caregivers.

These experiences, in turn, can cause worse outcomes, more pronounced deterioration in their health status, respiratory symptoms, or increased burden on the healthcare system (17).

The results of the anxiety control group applications of PSP patients were found to be high. Hyun Kyoung Lim et al. (3) found that young male PSP patients tended more to anxiety, depression, and personality traits. On the other hand, Sang-Hyuk Lee et al.'s (19) study showed that anger character could predict the pathophysiology of PSP. Eryiğit et al. (18) did not find a relationship between depression and PSP.

Manen et al.'s (20) study found that the prevalence of depression in COPD patients with severe airway obstruction (FEV1 <50%) was 25%, and they had a 2.5 times greater risk of depression than controls who were comparable for demographic variables and the presence of comorbidity. In patients with mild to moderate COPD, no increased risk for depression was seen.

According to the HAD questionnaire, it is noteworthy that the relapse rate in those with high anxiety scores was similar to that of the general PSP population but that the clinical admission of the patients with high scores were frequent.

The strength of the patients incorporated in the study is the analysis of 1-year clinical data. The group age dissimilarity between the patient population and the control required correction by covariance analysis. As we conducted this study in a single center, its validity, and broader applicability are limited. The study aimed to determine the prevalence of anxiety and depression disorders in patients with PSP. Our study suggests a higher incidence of anxiety attacks in PSP patients.

CONCLUSION

This study establishes a preliminary association between the incidence of anxiety and depression in patients with PSP. Anxiety and depression screening can help develop appropriate medical and psychosocial treatment programs, improve the quality of life for some patients, and reduce unnecessary hospital admissions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with permission of University of Health Sciences Ankara Atatürk Sanatorium Training and Research Hospital Ethics Committee (Date: 22.02.2023, Decision No: 2012-KAEK-15/2658).

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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YouTube as a source of patient information on positron emission tomography

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ABSTRACT

Aim: With the technological developments and the widespread use of smart phones, patients frequently use the internet to get information. YouTube is also one of the most popular sources for patient information. Positron emission tomography is one of the most common and important imaging methods specific to nuclear medicine. The aim of this study was to investigate the videos on YouTube about positron emission tomography imaging.

Material and Method: This study was conducted in October 2022. Videos were accessed on YouTube using the keywords "positron emission tomography" and "pozitron emisyon tomografisi". These videos were evaluated using the global quality scale (GQS), the DISCERN scale, and the Journal of the American Medical Association (JAMA) benchmark criteria.

Results: In total, 123 videos were reviewed and 75 videos were included in the study. Most of these videos were uploaded by non-physician person. The number of views, the number of comments, the number of video likes and the viewing rate of the non-physician sourced videos were found to be higher than the physician sourced videos. On the other hand, JAMA scores, GQS scores and DISCERN scores of non-physician sourced videos were found to be lower than physician sourced videos. These findings were statistically significant. In addition, significant positive correlations were found between JAMA score, GQS score and DISCERN score.

Conclusions: Widely used YouTube platform for any information. Patients and their relatives can also search specifically for any disease and treatment. Physicians and specialty associations can upload official videos to the YouTube platform to ensure that patients have access to higher quality and more accurate content. URLs of these videos can also be added to patient information forms.

Keywords: Video-audio media, quality control, nuclear medicine, information source, internet

INTRODUCTION

Positron emission tomography/computed tomography (PET/CT) is one of the most commonly performed and significant imaging modality specific to the nuclear medicine (1). PET/CT imaging using various radiopharmaceuticals is widely established in the diagnosis and follow-up of the oncological diseases. PET/CT frequently has a significant impact and contribution on the management of these patients (2). In addition PET/CT can detect molecular and metabolic changes before structural disorders and enables substantial contribution for prognostic information and disease recurrence (3).

Although the reasonability and the procedure of the PET/CT examination is explained to the patients by the primary clinician, it may not be fully understood and imagined by the patients. From the patient's point of view, PET/CT is an examination that they do not know much about, unlike conventional radiology. Before the examination, an informed consent form about the rationale of the procedure, possible side effects and radiation protection rules is inevitably taken. Despite all these information provided, some patients and their caregivers may be concerned about the procedure and may have desire for more information. For this purpose, they can use the internet to access free information easily. Internet access has become easier by widespread use and technological development of service provides, computers and smart phones. Therefore, it is popular to search online websites which can provide free and fast access to the information. In some studies, it has been reported that approximately 80% of internet users obtain medical information using the internet (4-6). In a few studies, it has been reported that approximately 75% of internet users are affected after searching for their illness on the internet (7, 8). However, the information obtained may be inaccurate, incomplete, irrelevant or biased (5, 9). One of the leading

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and common sources of online information for public is YouTube. New videos are constantly being uploaded to YouTube (10). The laxity of regulatory mechanisms in the video upload phase of YouTube raises doubts about the accuracy, reliability and quality of the uploaded content. This raises concerns about YouTube, which has significant potential in sharing medical information to public (5). In the literature, there are many studies that analyze the quality of the medical videos on YouTube (11-20). However, as far as we know, there is no similar study analyzing YouTube videos about PET/CT.

This study aims to assess the quality of video content by analyzing PET/CT related YouTube videos. Clarification of the quality and reliability of PET/CT related YouTube videos may enable directing patients and caregivers to the right sources, and can raise awareness for uploading scientifically reliable video content.

MATERIAL AND METHOD

This cross-sectional study was performed by using the 'YouTube' video-sharing website. The terms "positron emission tomography" and "pozitron emisyon tomografisi" were used for searching videos on October 2022. All procedures were carried out in accordance with the ethical rules and the principles. The options 'video' and 'sort by number of views' were selected as filters. All of the URLs received were recorded in an 'Excel' sheet and assessed by a nuclear medicine specialist experienced in this imaging modality. These searches were performed from a completely new account in Turkey to ensure that the search results are not affected by Youtube's existing algorithms for tailoring videos to certain people. The inclusion criteria were as follows: English videos on "positron emission tomography" and Turkish videos on "pozitron emisyon tomografisi". The exclusion criteria were as follows: Duplicate videos, inaccessible videos, contents unrelated to positron emission tomography, and videos in a language other than English and Turkish.

The duration of the video (seconds), the time passed since video upload (days), number of total views, total number of comments, number of comments per year, number of likes and dislikes, video like ratio [like/(like+dislike) ×100], video view ratio [number of views/days] were recorded during the evaluation procedure. Video power index (VPI) [like ratio×view ratio/100] which is used to determine the video popularity level was also calculated for each video.

The sources of the videos were analyzed into two categories as 'physician' and 'other than physician'. The quality of the videos was assessed by using the Journal of the American Medical Association (JAMA) benchmark criteria, the DISCERN Scale and the Global Quality Scale (GQS).

GQS is a 5 point instrument used to evaluate the quality, flow and ease of use for the video content as 1-2 points indicate low quality, 3 points indicate intermediate quality and 4-5 points indicate high quality (21).

The DISCERN scale is an instrument that consists of questions on the quality of information about treatment options, reliability and quality of the overall content. It has a score range of 0-80 points, with higher scores indicating the advanced level of quality (22).

JAMA benchmark criteria, which is used to evaluate the video reliability and accuracy, includes the parameters of 'authorship', 'attribution', disclosure' and 'validity' with 1 point assigned for the presence of each criterion. A score of 0 demonstrated poor reliability and accuracy; 4 points shows higher reliability and accuracy (23).

Since our study did not include any animal or human participants and the videos that incorporated in this study were accessible for everyone; the study did not require the approval of the ethics committee. There are similar studies with the same protocol in the literature (11, 13, 15).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Descriptive statistics specified numbers and percentages (%) for categorical variables. The mean and standard deviation were specified for the normally distributed continuous variables. The median was specified for continuous variables that did not show normal distribution. The conformity of the variables to the normal distribution was examined using histograms, probability charts, and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). Quantitative data according to the normal distribution characteristics were evaluated with the Mann Whitney U test or Student's t-test. Qualitative data were analysed with the chi-square test. The statistical significance level was chosen at a two-sided p-value of 0.05 or less.

RESULTS

A total of 123 videos (86 in English, 37 in Turkish) were assessed, and 75 videos (48 in English, 27 in Turkish) were included in the study according to the inclusion and exclusion criteria. Like ratio and video power index were excluded from the evaluation, as the number of dislikes for all the videos evaluated in our study was zero. Instead, only View ratio was used. While the source of 35 of these videos was physician, the source of 40 of them was non-physician. Examined videos were divided into three groups according to their GQS scores

as low, intermediate and high quality. Seven videos were rated as low quality, 32 as intermediate quality, and 36 as high quality. The classification of the content of the videos according to the video source and quality is summarized in **Table 1**.

The number of days since the upload of all videos, the length in seconds, the number of views, the number of comments, the number of likes, the number of comments per year, view ratio, Jama score, GQS score, Discern scores and quality classes are summarized in **Table 2**.

Table 1. The classification of the content of the videos according to the video source and quality

Content\Quality	Source						Total
	Physician			Non-physician			
	Low	Intermediate	High	Low	Intermediate	High	
How does it work?	0	1	1	1	5	4	12
How to imaging?	0	0	3	2	6	6	17
What to do before and/or after?	0	0	4	0	1	2	7
What is PET/CT?	2	6	5	0	5	1	19
What are the advantages?	0	2	4	0	1	1	8
Where to use?	1	1	5	1	4	0	12
Total	3	10	22	4	22	14	75

PET/CT positron emission tomography/computerized tomography

Table 2. General features of videos

	All (n:75)	Video Source		p value (physician vs. non-physician)
		Physician (n:35)	Non-physician (n:40)	
Time after upload (day)				
Mean±SD	2338±1323	2177±1386	2479±1265	0.367
Range	95-5009	95-4970	153-5009	
Video duration (second)				
Mean±SD	296±249	315±285	279±215	0.633
Range	52-1196	52-1196	74-1031	
Number of video views				
Mean±SD	97963±169557	39555±59447	149070±213844	<0.001
Range	916-962467	916-264060	1743-962467	
Number of comments				
Mean±SD	22.86±49.60	10.57±21.27	33.62±63.39	0.002
Range	0-360	0-110	0-360	
Number of video likes				
Mean±SD	588±1448	155±282	967±1895	<0.001
Range	0-9200	0-1400	0-9200	
Number of comments per year				
Mean±SD	6.45±16.84	4.09±9.22	8.52±21.32	0.034
Range	0-101	0-47	0-101	
View Ratio				
Mean±SD	44.05±62.37	29.57±51.32	56.72±68.79	0.004
Range	0.25-288.34	0.25-265.39	0.93-288.34	
JAMA score				
Mean±SD	2.54±0.59	2.91±0.50	2.22±0.47	<0.001
Range	1-4	1-4	1-3	
GQS				
Mean±SD	3.43±0.77	3.66±0.80	3.23±0.69	0.014
Range	1-5	2-5	1-4	
Discern Part 1				
Mean±SD	18.92±5.11	20.37±4.95	17.65±4.97	0.013
Range	9-33	11-30	9-33	
Discern Part 2				
Mean±SD	19.25±5.60	20.51±5.63	18.15±5.41	0.072
Range	7-30	10-30	7-29	
Discern Part 3				
Mean±SD	3.24±1.03	3.60±1.00	2.92±0.97	0.004
Range	1-5	2-5	1-5	
Total Discern score				
Mean±SD	41.38±11.10	44.42±10.89	38.72±10.71	0.025
Range	17-63	23-63	17-63	
Quality, n (%)				
Low	7 (9.3%)	3 (4.0%)	4 (5.3%)	0.047
Intermediate	32 (42.7%)	10 (13.3%)	22 (29.3%)	
High	36 (48.0%)	22 (29.3%)	14 (18.7%)	

SD standard deviation, JAMA Journal of the American Medical Association benchmark criteria, GQS global quality scale

Of the physician sourced videos, 3 were low quality, 10 were medium quality, and 22 were high quality. In videos of non-physician sourced, these numbers were 4, 22, 14, respectively (p: 0.047). The number of views, the number of comments, the number of likes, the number of comments per year, and the View ratio of the physician sourced videos were found to be significantly lower than the non-physician sourced videos. Jama scores, GQS scores, Discern Part 1 and Part 3 scores and total discern scores of physician sourced videos were found to be significantly higher than non-physician sourced videos.

The data of the videos analyzed by quality groups and languages are summarized in **Table 3**.

The number of views, the number of comments, the number of likes, the View ratio, Discern Part 1 and Part 2, and the total Discern scores of the English-language videos were found to be significantly higher than the Turkish-language videos. The number of views of the videos was found to be highest in the intermediate quality group with an average of 104,495.

Correlation analyzes were also performed between the data obtained in our study. There was moderate positive correlation between JAMA score and GQS score, weak positive correlation between JAMA score and Total Discern score, and high positive correlation between GQS score and Total Discern score (**Table 4**). No significant correlation was found in the separate correlation analyzes performed with JAMA score, GQS score, Total Discern scores with number of views, number of comments, number of likes, number of comments per year and view ratio.

Table 3. General features of videos according to quality and language

	Quality			p value	Language		p value
	Low	Intermediate	High		English	Turkish	
Time after upload (day)							
Mean±SD	1762±1440	2477±1338	2327±1294	0.427	2743±1276	1618±1092	<0.001
Range	153-3711	95-5009	193-4970		193-5009	95-3711	
Video duration (second)							
Mean±SD	278±337	247±179	343±280	0.179	330±261	236±218	0.020
Range	74-1031	52-872	92-1196		76-1196	52-1138	
Number of video views							
Mean±SD	42487±68825	104495±195426	102945±159583	0.337	132870±198687	35908±64932	<0.001
Range	916-186506	1743-962467	1130-808329		7040-962467	916-264060	
Number of comments							
Mean±SD	16.42±16.39	20.43±34.03	26.27±64.06	0.693	28.56±58.88	12.74±23.85	0.023
Range	1-40	0-136	0-360		0-360	0-110	
Number of video likes							
Mean±SD	371±654	351±561	840±1988	0.761	857±1754	109±175	<0.001
Range	22-1800	0-2100	0-9200		0-9200	4-724	
Number of comments per Year							
Mean±SD	17.08±34.704	3.41±5.25	7.10±18.37	0.293	5.29±14.75	8.51±20.17	0.457
Range	0-95	0-22	0-101		0-101	0-95	
View Ratio							
Mean±SD	24.23±23.45	40.72±59.42	50.87±49.76	0.792	50.00±64.85	33.47±57.33	0.011
Range	0.25-66.47	0.93-288.34	0.44-265.39		1.81-288.34	0.25-265.39	
JAMA score							
Mean±SD	2.00±0.57	2.28±0.52	2.88±0.46	<0.001	2.50±0.54	2.62±0.68	0.217
Range	1-3	1-3	2-4		2-4	1-4	
Discern Part 1							
Mean±SD	12.57±3.10	16.15±3.36	22.61±3.83	<0.001	20.02±4.95	16.96±4.90	0.018
Range	9-18	11-25	16-33		11-33	9-25	
Discern Part 2							
Mean±SD	12.14±2.91	16.56±4.25	23.02±4.19	<0.001	20.22±5.12	17.51±6.09	0.045
Range	7-16	10-26	14-30		12-30	7-30	
Discern Part 3							
Mean±SD	2±0.57	2.56±0.61	4.08±0.64	<0.001	3.29±1.03	3.14±1.06	0.655
Range	1-3	2-4	3-5		2-5	1-5	
Total Discern score							
Mean±SD	26.71±5.05	35.28±7.32	49.66±7.80	<0.001	43.54±10.40	37.55±11.44	0.028
Range	17-32	23-51	35-63		26-63	17-57	

SD standard deviation, JAMA Journal of the American Medical Association benchmark criteria, GQS global quality scale

Table 4. Correlation relationship between JAMA, GQS and Total Discern

	p	r
JAMA vs GQS	<0.001	0.589
JAMA vs Total Discern	<0.001	0.463
GQS vs Total Discern	<0.001	0.781

JAMA Journal of the American Medical Association benchmark criteria, GQS global quality scale

DISCUSSION

PET is far the most important imaging modality of nuclear medicine for oncological diseases (2). Because of the patients directed to PET/CT exam are mostly worried about their own health at the appointment, they may not benefit enough from the verbal and written information given. Patients and caregivers may seek alternative ways to learn more about the rationale of this unfamiliar imaging and radiation exposure. Today, internet research and especially search of YouTube constitutes the majority of these alternative ways.

In our study, PET/CT related videos on YouTube were evaluated and analyzed. Most of them were uploaded by non-physicians. The number of views, the number of comments, the number of video likes and the view ratio of the videos of non-physician sourced were found to be higher than the videos of physician sourced. On the other hand, JAMA scores, GQS scores and DISCERN scores of non-physician sourced videos were found to be lower than physician sourced videos.

In a study by Şan (20), the quality of 270 YouTube videos about 'radionuclide treatments' were evaluated. While the best quality videos were found to be physician sourced, it was seen that the most watched and highest VPI videos were non-physician sourced videos. Consistent with our study, the average number of views, the number of comments, the number of annual comments, the number of video likes, and the VPI values of physician sourced videos were found to be lower than non-physician sourced videos. JAMA scores, GQS scores and DISCERN scores were found to be higher in physician sourced videos.

In another study of Şan (19), YouTube videos related to 'radioactive iodine treatment' were evaluated. Similar to our study, the average number of comments, annual number of comments, number of likes, number of views, and VPI values of physician sourced videos were found to be lower than non-physician sourced videos. In this study, a classification was made according to the video languages. While the number of views, the number of likes, the number of comments and the number of annual comments of the English language videos were found to be higher than the Turkish language videos, there was no difference between the JAMA scores, GQS scores, Discern scores and VPI values. In our study, the number of views, the number of comments and the number of likes of the English language videos were found to be higher, in line with these results. However, contrary to aforementioned study, the VPI values, JAMA scores and DISCERN scores of the videos in English were also found to be higher than the videos in Turkish. This inconsistency may be due to more careful and scientific preparation of the content of those videos.

In a study examining the role of YouTube videos in informing patients in myofascial pain syndrome, 186 videos were analyzed (17). Contrary to our study, physician sourced videos were the most watched and commented videos.

YouTube is a free social platform and anyone can upload videos with random content. As in every field, there are many videos with medical information that is not checked for appropriate content (5). It is important for the medical videos to pass certain filters of quality in order not to mislead public. For this purpose, content of medical videos may be evaluated with any of the parameters of JAMA, GQS and DISCERN. Studies have reported that there is a high positive correlation between these three parameters (18-20). In our study, significant positive correlations were found between JAMA score, GQS score, and DISCERN score.

In our study, we divided the videos into quality groups according to the GQS scores. Videos with a score of 1-2 were evaluated as low quality, 3 as intermediate quality, and 4-5 as high quality. In the study of Koçyiğit et al. (14), Youtube videos were examined as a source of information for ankylosing spondylitis and most of the videos were for found high-quality (48.2%). In another study, Youtube videos about COVID-19 and rheumatological diseases were analyzed, and 41.4% of the videos were found as high quality (15). Similar to these studies, we found that 36 (48.0%) of the 75 videos included in our study were of high quality. However, there are also studies in the literature in which most of the videos are evaluated as low quality (12, 17, 19) and medium quality (20), which is inconsistent with these findings .

In the study of Koçyiğit et al. (14), the videos grouped according to their quality and found to be similar in terms of video views, video likes and video comments. There was a significant difference between the groups in terms of DISCERN score. Since DISCERN score also reflect the video quality, it is natural that there is a significant difference between the groups. In the study analyzing YouTube videos about myofascial pain syndrome, the most popular, most liked and most watched videos were medium quality. In that study, the least popular, least liked and least watched videos were high quality (17). In the study of Şan (19), analyzing the radioactive iodine treatment related YouTube videos, the

the most liked, commented and the videos with highest VPI was the medium quality group. In that study, the group with the lowest popularity, number of views and likes was the high quality group. In our study, the highest number of views was in the medium quality group, while the number of comments, number of likes and view ratio (VPI) were the highest in the high quality group. However, these differences between the quality groups in our study were not statistically significant. In line with our findings, Zengin et al. (11) examined YouTube videos on musculoskeletal ultrasound training and found the medium quality videos as the most viewed videos. In addition, they found the high quality group as the most liked and with the highest VPI.

Information given to patients and caregivers may not be effective because of reduced attention due to momentary stress of their disease and radiation exposure concern. In addition, PET/CT imaging is less known compared to conventional radiology. They may use social platforms such as YouTube, where they can access almost any true or unreal information. In our study, most of the YouTube videos were non-physician sourced and these were of lower quality than physician sourced videos. Paradoxically, they were watched and liked more, and their view ratio were higher. There are similar studies in the literature in which physician sourced videos constitute the majority (18). In these studies, non-physician sourced videos with less quality were evaluated as the most popular, the most liked, and the most watched videos. It may be beneficial to upload official videos of specific physician associations in order to sharing videos with higher quality content to public. Although there are studies in the literature stating that medium quality and low quality videos constitute the majority, most of the videos we examined in our study were high quality videos, but the total of low and medium quality videos was still higher (n: 39). This may lead to incorrect and/or incomplete information shared to patients. For this reason, on YouTube platform with careless control mechanism for upload, significant need for medical related videos to pass qualified filters.

Study Limitations

Our study includes some limitations. We were not able to evaluate all PET-related videos and only analyzed some of the videos in Turkish and English. Most of the videos we included in our study consisted of videos in English language. These videos were significantly higher in terms of the number of views, the number of likes, view ratios and DISCERN score compared to the videos in Turkish. This may be due to the fact that videos in English can reach more people in the world. If videos in other languages were also included in the evaluation, the results may be changed.

CONCLUSION

On YouTube platform is widely used for any information and patients and their caregivers can also search for any disease and treatments especially. Physicians and speciality associations may upload official videos to YouTube platform and add URL's to patient information forms so that patients may access better quality and more accurate content.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study does not require an ethics committee.

Informed Consent: This study does not require an informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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Original Article

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Evaluation of pituitary gland dimensions by age and gender in healthy individuals in the Turkish population

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ABSTRACT

Aim: Evaluating pituitary gland dimensions in varying age ranges and genders is essential for determining average values in MRI examinations. Therefore, the main objective of our study is to create normative data for pituitary gland size in the Turkish population.

Material and Method: Anteroposterior (AP), transverse (TR), and craniocaudal (CC) dimensions of the pituitary glands of 200 patients over 18 years of age, who underwent Brain MRI examination in our centre between November 2022 and March 2023, did not have any known endocrine disease, did not use hormonal therapy, were not pregnant or breastfeeding, had no history of radiotherapy or chemotherapy were measured from their sagittal and axial MRI sequences. The Kolmogorov-Smirnov test was used for normality analyses. The Mann-Whitney U test was used to compare the non-normally distributed numerical variables between the two groups. Spearman correlation was applied to determine the relationship between age and pituitary gland measurement values.

Results: Anteroposterior and craniocaudal measurements of the pituitary gland of female patients included in the study were significantly higher than males ($p=0.011$ and $p<0.01$, respectively). When the patients under 50 years of age and those aged 50 and over are grouped, anteroposterior, transverse, and craniocaudal measurements were found to be significantly higher in the group under 50 years old ($p<0.001$). When the patient groups between 18-29 and 30-49 were compared, anteroposterior, transverse, and craniocaudal measurements were higher in the group between 18-29 ($p<0.01$, $p<0.001$, and $p=0.026$, respectively).

Conclusion: This work gives normative data that may simplify the examination of the pituitary gland in neuroendocrine diseases. It also reveals that gender-specific changes in pituitary size and shape accompany aging. Changes related to race, age, and gender should be kept in mind.

Keywords: Magnetic resonance imaging, normal pituitary gland, sella turcica

INTRODUCTION

Since the proper growth of the pituitary gland is based on neuroendocrine changes that vary throughout life, pituitary gland height and volume naturally vary by age and gender (1,2). Most Magnetic Resonance Imaging (MRI) studies on the normal physiological development of the adolescent and adult pituitary gland size agree that the size peaks somewhere in the second or third decade of life and then decreases in both men and women (2-5).

However, there are inconsistent findings regarding those over 50 years of age. Many studies have shown that women's pituitary glands are more prominent in the 6th and 7th decades than that men's (1,2,4,6). Some studies even suggest that pituitary gland size increases in women over 50. It has been recommended that this is due to the increase in gonadotropic hormone levels due to the absence of negative feedback from gonadal steroids in the postmenopausal period (2-6). In contrast, many studies show that men in this age range have larger pituitary glands than women, and even one study shows an increase in pituitary size in men (5,7).

These studies show that changes in the endocrine environment can cause changes in pituitary gland morphology, such as an increase in pituitary gland height during adolescence (1,8) followed by an age-related decrease in size (9).

Therefore, evaluating pituitary gland dimensions in varying age ranges and genders is essential for determining average values in MRI examinations. Therefore, the main objective of our study is to create normative data for pituitary gland size in the Turkish population.

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MATERIAL AND METHOD

Patient Selection and Evaluation

The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-invasive Clinical Researches Ethics Committee (Date: 09.03.2023, Decision No: 2023-03/27). All procedures were carried out under the ethical rules and the principles of the Declaration of Helsinki. Furthermore, consent was obtained from all patients in the study before the MRI examination.

The images and clinical histories of the patients who underwent brain MRI examinations in our centre between November 2022 and March 2023 were evaluated retrospectively. Patients under 18 with a history of endocrine disease, patients using hormonal therapy, patients during pregnancy or breastfeeding, and patients with a history of chemotherapy or cranial radiotherapy were excluded from the study. As a result, pituitary gland anteroposterior (AP), transverse (TR), and craniocaudal (CC) dimensions were measured from the sagittal and axial post-contrast T1 MRI sequences of 200 patients. The sample measurement is presented in **Figure 1**.

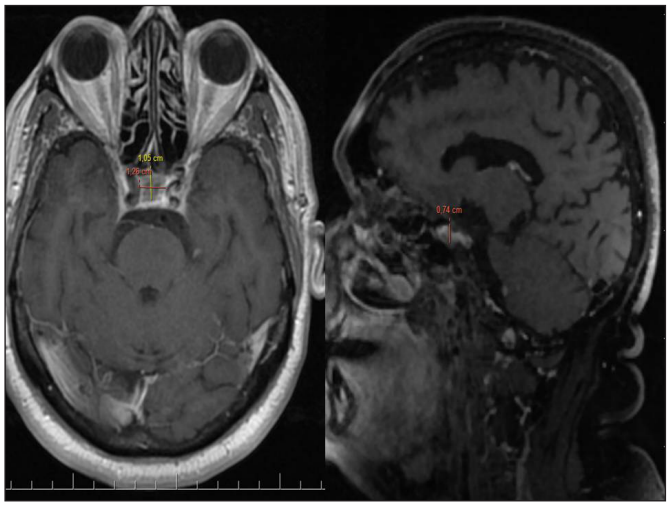

Figure 1. Pituitary gland size measurement in a sample case.

Gland size range and median values were determined and presented by age groups (18-29, 30-49, and above 50 years). Age groups were determined by taking the groupings made in previous studies as an example(10).

Statistical Analysis

All analyses were performed with SPSS 25.0 (IBM®, USA). The findings of the study are presented as frequency and percentages. The Kolmogorov-Smirnov test was used for normality analyses. Numerical variables that do not show normal distribution are presented as the median and interquartile range (IQR:25-75 percentile). The Mann-Whitney U test was used to compare the non-normally distributed numerical variables between the two groups. Spearman correlation was applied to determine the relationship between age and pituitary gland measurement values. For statistical significance, $p < 0.05$ was accepted as significant.

RESULTS

Age, gender, and pituitary gland anteroposterior, transverse, and craniocaudal measurement values of the patients participating in the study are shown in **Table 1**.

Table 1. Age, gender and pituitary gland anteroposterior, transverse, and craniocaudal measurement values of the patients

Age (Median, IQR:25-75 p)	55.0 (42.0-64.8)
Gender (n/%)	
Female	129 (64.5)
Male	71 (35.5)
Pituitary gland measurements (Median, IQR:25-75 p)	
Anteroposterior	8.5(7.4-9.5)
Transverse	13.1 (11.6-14.6)
Craniocaudal	5.7 (4.9-6.7)

IQR: Interquartile range

Anteroposterior and craniocaudal measurements of the pituitary gland of female patients included in the study were significantly higher than males (p=0.011 and p<0.01, respectively). However, there was no significant difference between pituitary gland transverse measurements by gender (p=0.123) (**Table 2**).

Table 2. Age and pituitary gland anteroposterior, transverse, and craniocaudal measurement values by gender

	Female (n=129)	Male (n=71)	p
Age (Median, IQR:25-75 p)	51.0 (41.5-62.0)	62.0 (41.0-71.0)	
Pituitary gland measurements (Median, IQR:25-75 p)			
Anteroposterior	8.7 (7.5-9.7)	8.0 (7.1-9.0)	0.011
Transverse	13.1 (11.8-14.6)	12.3 (10.8-14.6)	0.123
Craniocaudal	5.9 (5.3-6.7)	5.3 (4.6-6.4)	<0.01

IQR: Interquartile range

A negative correlation was detected between age and pituitary gland are anteroposterior (Rho=-0.765, p<0.001), transverse (Rho=-0.709, p<0.001), and craniocaudal (Rho=-0.777 p<0.001) measurements. When the patients under 50 years of age and those aged 50 and over are grouped, anteroposterior, transverse, and craniocaudal measures were found to be significantly higher in the group under 50 years old (for all measurement values p<0.001). When the patient groups between 18-29 and 30-49 were compared, anteroposterior, transverse, and craniocaudal measurements were higher in the group between 18-29 (p<0.01, p<0.001, and p=0.026, respectively). Pituitary gland measurement values by age group are shown in **Table 3**.

Table 3. Pituitary gland measurement values by age groups

	18-29 years (n=24)	30-49 years (n=54)	≥50 years (n=122)
Pituitary gland measurements (median; IQR:25-75p)			
Anteroposterior	10.3 (9.8-11.0)	9.2 (8.7-10.0)	7.7 (6.7-8.5)
Transverse	15.8 (14.9-16.6)	14.4 (13.1-15.0)	11.8 (10.5-13.1)
Craniocaudal	7.0 (6.7-7.6)	6.7 (5.9-7.3)	5.2 (4.5-5.7)

IQR: Interquartile range

DISCUSSION

The pituitary gland was first described anatomically in 1543 by Belgian scientist Andreas Vesalius (11). Despite its small size, slight changes in the pituitary gland can cause significant effects on other neuroendocrine organs. Although pituitary gland contour or sella turcica width is rapidly evaluated in radiological evaluation, this evaluation may be misleading due to changes in pituitary gland size and shape depending on age, gender, and race. In addition, sella size is not a sensitive parameter in evaluating pituitary gland abnormalities (since conditions such as empty sella can also cause sella turcica enlargement) (12-14).

In addition to providing information about pituitary gland functional status, gland dimensions are critical in evaluating, diagnosing, and prognosis of intracellular masses and pituitary gland tumours (15). For example, Suzuki et al. (16) have shown that height measurements above 9 mm in females and 8 mm in males reflected abnormal pituitary gland findings.

Studies have reported that pituitary gland sizes vary in age groups, races, and gender (17). Age-related size changes have been associated with changes in the hormonal cycle at different ages. In addition, some studies have revealed significant differences in gland sizes between genders and that gland sizes are significantly higher in females (9).

Due to this complex hormonal cycle and age, gender, and race-related changes, it is clinically and radiologically essential to know the standard pituitary gland sizes. Unfortunately, although normative data studies are conducted on different races in the literature (11,18), few studies are shown on the Turkish population (18-20).

In our study with the Turkish population, pituitary gland measurements in females were statistically significantly higher than in males, especially more prominent in the AP and CC axis. In addition, pituitary gland dimensions were found to be considerably higher in people under the age of 50 compared to those over the age of 50. When the patient group under 50 was examined in 18-29 and 30-49, a significant height was found in all measurements (AP-TR-CC) in the 18-29 age group. In addition, gland size range and median values were determined and presented by age groups (18-29, 30-49, and above 50 years).

Our study is one of the few studies conducted with the Turkish population, and diameter measurements that can be made by each radiologist in each centre can help the radiological and clinical evaluation of the gland. In addition, knowing the average range measurements determined by age groups can give an idea about the functional status of the gland. The limitation of our study is the small number of samples and the retrospective nature of the study. Another area for improvement was the stage of the menstrual cycle information is not available in our study. Studies with more extensive series to be prospectively conducted in the future should be conducted.

CONCLUSION

This work gives normative data that may simplify the examination of the pituitary gland in neuroendocrine diseases. It also reveals that gender-specific changes in pituitary size and shape accompany aging. Changes related to race, age, and gender should be kept in mind.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-invasive Clinical Ethics Committee (Date: 09.03.2023, Decision No: 2023-03/27).

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 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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Demographic and clinical characteristics of patients with nonspecific esophageal motility disorder

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ABSTRACT

Aim: Although nonspecific esophageal motility disorder(NEMD) is the most common diagnosis in manometry, unlike other primary esophageal disorders, it is the least known and least studied disorder in the literature. Studies with a small number of patient groups have been reported in the literature. The aim of this study is to share the demographic and clinical characteristics of the single center high-volume NEMD patients we have followed up.

Material and Method: The study was carried out retrospectively by examining the motility records of 391 patients diagnosed with NEMD in the motility laboratory of the gastroenterology clinic of our hospital. 20-year motility laboratory records between 1991 and 2019 were reviewed.

Results: The mean age of 391 patients diagnosed with NEMD was 49.08±14.4 (18-90). 213 (54.5%) of them were female, and 178 (45.5%) of them were male. The primary symptom was reflux in 56.8% (222/391) of the patients, and dysphagia in 43.2% (169/391). While there was no esophagitis in 78.2% of the patients who had endoscopy, esophagitis was found in 21.8% of them. Pathological reflux was detected in 73.5% of the patients whose 24-hour pH was measured. In the repeated manometry results of patients due to increased complaints in their follow-up whose initial manometry findings were compatible with NEMD, 18 patients were diagnosed with achalasia, 5 patients with nutcracker esophagus, and 4 patients with diffuse esophageal spasm (DES).

Conclusion: The majority of patients with NEMD are associated with reflux. Patients with NEMD who do not have endoscopic and radiological organic disorders should be re-evaluated with manometry and further examinations if their complaints persist.

Keywords: Nonspecific esophageal motility disorder, esophageal manometry, gastroesophageal reflux

INTRODUCTION

Motility disorders that are not associated with causes such as esophageal stenosis or cardia tumor and that are not caused by neurological, muscular or other systemic disorders are called primary esophageal motility disorders. In conventional manometry, primary esophageal motility disorders are classified as achalasia, diffuse esophageal spasm (DES), nutcracker esophagus, hypertensive and hypotensive lower esophageal sphincter and nonspecific esophageal motility disorder (NEMD) (1,2). While the diagnostic criteria of primary esophageal motility disorders other than NEMD are certain, those that cannot be classified according to a certain criterion are called NEMD (2,3). Findings in conventional esophageal manometry that cannot be classified in other known primary motility disorder criteria, non-conducted contractions (>20%) in response to wet swallowing, retrograde contractions, repetitive contractions (>2 peaks), low amplitude contractions (<30 mm Hg), prolonged contraction time (>6 secs), high amplitude contractions (>180 mm Hg), spontaneous contractions, incomplete lower esophageal sphincter (LES) relaxation are called NEMD (1-5).

Although NEMD is the most common diagnosis in manometry (1,2), unlike other primary esophageal disorders, it is the least known and least studied disorder in the literature. Studies with a small number of patient groups have been reported in the literature. The aim of this study is to share the demographic and clinical characteristics of the single center high-volume NEMD patients we have followed up.

MATERIAL AND METHOD

Patients

The study was carried out retrospectively by examining the motility records of 391 patients diagnosed with NEMD in the motility laboratory of the gastroenterology clinic of our hospital. After obtaining approval from the

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Ankara Bilkent City Hospital No: 2 Clinical Researches Ethics Committee (Date: 01.03.2023, Decision No: E2-23-3579), the motility laboratory records between 1991 and 2019 were reviewed. Demographic characteristics of the patients, complaints at admission, 24-hour pH meter and esophageal manometry results were evaluated. Those younger than 18 years of age, those with another primary esophageal motility disorder, those with rheumatologic or systemic disorder that may involve the esophagus, patients with organic disorders in the esophagus, and those with a history of esophagus and stomach surgery for any reason were excluded from the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Manometry Protocol

After 8 hours of fasting, the manometric catheter was inserted nasally into the stomach. Esophageal motility was assessed using conventional esophageal manometry (Dentsleeve; Dentsleeve International, Mui Scientific, Mississauga, Ontario, Canada). Conventional manometry uses an 8-channel polyvinyl catheter with a Dent sleeve. The catheter is placed in the lower esophageal sphincter (LES) and sensors evaluate LES relaxation and pressure and esophageal contractions. After the sleeve area of the catheter was placed in the lower esophagus, esophageal motor functions were assessed with 10 wet swallows at 20-second intervals and the results were interpreted according to the recommendations of the American Gastroenterological Association (6-8).

pH Monitoring Protocol

Use of medications that could affect the gastric pH of the patient was terminated 7 days before the procedure and 24-h esophageal pH monitoring was performed after 8 hours of fasting. The distal sensor of the PHI15/PHN15 dual pH catheter (Sandhill Scientific Inc., Highlands Ranch, CO, USA) was placed 5 cm above the LES and 20 cm above the proximal sensor. A pH monitor was used to record findings for 24 hours after the catheter was fixed in the nose. The presence of distal and proximal reflux was investigated and the results were interpreted according to the recommendations of the American Gastroenterological Association (7,8).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Among the numerical variables, those with normal distribution are shown as mean±standard deviation, and those with normal distribution are shown as median (min-max). Categorical variables are expressed as numbers and percentages.

RESULTS

The mean age of 391 patients diagnosed with NEMD was 49.08±14.4 (18-90). Of these, 213 (54.5%) were female, and 178 (45.5%) were male. The primary symptom was gastroesophageal reflux in 56.8% (222/391) of the patients, and dysphagia in 43.2% (169/391). While there was no esophagitis in 78.2% of the patients who had endoscopy, esophagitis was found in 21.8% of them. Pathological reflux was detected in 73.5% of the patients whose 24-hour pH was measured. In the repeated manometry results of patients (due to increased complaints in their follow-up) whose initial manometry findings were compatible with NEMD, 18 patients were diagnosed with achalasia, 5 patients with nutcracker esophagus, and 4 patients with DES (**Table 1**).

Table 1. Demographic and characteristics of the patients

Gender	
Female (%)	213 (54.5%)
Male (%)	178 (45.5%)
Mean Age (years)	49.08±14.4 (18-90)
Application complaint	
Dysphagia	43.2% (169/391)
Reflux symptoms, %,n	56.8% (222/391)
Esophagitis	
Endoscopy report could not be reached in 180 patients	
In the endoscopy of 211 patients	
No esophagitis	78.2%
Grade A esophagitis	10.9%
Grade B esophagitis	9.9%
Grade C esophagitis	1%
pH meter	
Reflux was not studied in 195 patients	
Reflux was studied in 196 patients	
Has pathological reflux	73.5% (144/196)
No pathological reflux	26.5% (52/196)
Mean LESP (mmHg)	15.6±11.91
End of follow-up	
Achalasia	18
Nutrcacker esophagus	5
Diffuse esophageal spasm	4

LESP: Lower esophageal sphincter pressure

Evaluating the contractions in the esophageal body in manometry, 71.3% of the patients had normal peristalsis, 28.7% of them had non-peristaltic contractions. In 63.4% (248/319) of them, the contraction amplitude of the esophageal body was low (< 30 mmHg). Some contractions were not transmitted distally in 70 patients and interrupted contractions were detected in 26 patients. In addition, 97 (67.4%) of 144 patients with pathological reflux on a 24-hour pH meter had low esophageal body contraction amplitude (**Table 2**).

Table 2. Evaluation of contraction amplitudes in theesophageal body in manometry.

	Patients, n (%)
Peristaltic contraction	279 (71.4%)
Non-peristaltic contraction rate	112(28.6%)
≤ 30%	48
40-50%	45
≥60	19
Normal amplitüde contraction	138 (35.3%)
Low amplitude contraction	248 (63.5%)
High amplitude contraction	5 (1.2%)
10% contraction	2
20% contraction	2
30% contraction	1
Interruptered contraction	26
≤ 30%	19
40-50%	7
Nontransmitted contraction	70
≤ 30%	52
40-50%	18
Normal contraction duration	380 (97.2%)
Prolonged contraction	11 (2.8%)
Mean contraction duration	10.36±1.53 (8-13.5)
Tripled-peaked contraction	6
Complete LES relaxation	307 (78.6%)
Incomplete LES relaxation	79 (20.2%)
≤ 30%	11
40-50%	25
≥60	43
Noncomplete LES relaxation contraction (only 10% noncomplete relaxation)	5 (1.2%)

LES: Lower esophageal sphincter

The pH meter was studied in 161 of 222 patients whose primary complaint was reflux, and the procedure could not be performed in 61 patients because they did not accept or tolerate the pH meter. In 35 patients, whose primary complaint was dysphagia and who also had reflux symptoms, manometry was performed first, and a pH meter was also performed upon detection of NEMD in manometry. As a result, the pH meter results of a total of 196 patients were examined. Pathological reflux was detected in 144 (73.5%) of the patients whose 24-hour pH values were measured (Pathological reflux was detected in the distal esophagus in 102 patients and in the proximal and distal esophagus in 42 patients). Comparing the demographic characteristics to esophageal manometry findings of patients with and without reflux in patients whose 24-hour pH values were measured, statistically more reflux was found in males than in females. No significant correlation was found between other findings in manometry and reflux (**Table 3**).

Manometry was performed again in 87 patients due to the persistence of their complaints. As a result of repeated manometry, 18 patients were diagnosed with achalasia, 5 patients with nutcrucker esophagus, and 4 patients with diffuse esophageal spasm. 18 patients who were initially diagnosed with NEMD were diagnosed with achalasia after 1 to 4 years of follow-up, and they undergone balloon dilatation therapy. In the initial manometry of the patients diagnosed with achalasia, LESP was greater than 45 mmHg in 5 patients, and LES relaxation was normal in 11 patients; 7 of them had >20% incomplete swallowing relaxation, and >20% of esophageal wet swallows were aperistaltic in 9 of them; 7 of them had contraction amplitudes less than 30 mmHg at >20% swallowing, only 1 patient had contraction amplitudes averaging 240 mmHg in 30% of swallows. Due to the increasing complaints of this patient, type 3 achalasia was diagnosed by repeat manometry performed in the center where high-resolution manometry was performed. (**Table 4**).

Table 3. Manometric and demographic characteristics of patients with reflux studied.

n= 196	Reflux positive (n=144, 73.5%) (n)(%)	Reflux negative (n=52, %26.5) (n),(%)	p
Gender			
Female (n=112)	76 (67.9)	36 (32.1)	0.04
Male (n=84)	68 (81)	16 (19)	
Mean age (years)	46.9±13.02	48.5±14.0	0.52
LESP (mmHg)	14.36±10.65	14.86±12.7	0.78
Non-peristaltic contraction			
Yes (n=48)	38 (79.2)	10 (20.8)	0.3
No (n=148)	106 (71.6)	42 (28.4)	
Incomplete LES sphincter relaxation			
Yes (n=26)	18 (69.2)	8 (30.8)	0.59
No (n=170)	126 (74.1)	44 (25.9)	
Interruptered contraction			
Yes (n=13)	11 (84.6)	2 (15.4)	0.52
No (n=183)	133 (72.7)	50 (27.3)	
Nontransmitted contraction			
Yes (n=40)	32 (80)	8 (20)	0.32
No (n=156)	112 (71.8)	44 (28.2)	

LESP: Lower esophageal sphincter pressure, LES: Lower esophageal sphincter

Table 4. Initial manometry findings of patients diagnosed with achalasia in their follow up.

Gender	
Female, n (%)	12 (66.7%)
Male, n (%)	6 (33.3%)
Mean age (years)	50.44±11.52 (35-80)
Application complaints	
Dysphagia, n(%)	12 (66.7%)
Reflux symptoms, n(%)	6 (33.3%)
The mean time for patients to be diagnosed with achalasia (years)	1.72±0.89 (1 – 4)
Mean LESP (mmHg)	30 ±15.43
Normal (10 – 45 mmHg), n,(%)	13 (72.3%)
High (> 45 mmHg) , n,(%)	5 (27.7%)
LES relaxation	
Normal relaxation, n (%)	11 (61.1%)
Incomplete relaxation, n (%)	7 (38.9%)
Normal peristaltic contraction, n (%)	9 (50%)
Non-peristaltic contraction, n (%)	9 (50%)
Normal amplitude contraction	10 (55.6%)
Low amplitude contraction, n (%)	7 (38.9%)
High amplitude contraction, n (%)	1 (5.5%)

LESP: Lower esophageal sphincter pressure, LES: Lower esophageal sphincter

DISCUSSION

Although NEMD was identified by Sanderson et al. (9) in 1967, few studies have been reported in the literature on its clinical significance or course.

Our study showed that this disorder is mostly seen in middle aged persons, and it is seen a little more in women. Patients mostly present with reflux-like symptoms or dysphagia. In approximately two-thirds of patients, the esophagus is exposed to pathological acid exposure.

GERD-associated motility abnormality has been classified as NEMD in some studies (2, 10). NEMD is mostly named as ineffective esophageal motility (IEM) according to the Chiago classification in high resolution esophageal manometry (2, 11, 12). It is still controversial whether NEMD is a primary esophageal motility disorder or whether the abnormality is secondary to acid-induced pathological damage to the esophagus. It has been shown that disorders in esophageal motility (absent or incomplete contractions, weak contractions) play a role in the pathogenesis of GERD (11, 13). In a study (2), 52.8% of reflux patients had NEMD, 43.8% had normal manometry findings, and 4% had nutcracker esophagus. As seen in this study, NEMD was detected in 94% of GERD patients with abnormal esophageal motility. Again in this study, more severe acid exposure was reported in 24-hour pH meters of patients with NEMD. In our study, we found reflux in approximately three-fourths (73.5%) of NEMD patients whose reflux was studied, and reflux was even higher in males. Considering the prevalence of reflux normally seen in the community, NEMD is largely associated with reflux, as seen in our study.

Contrary to studies (14,15) claiming that abnormal esophageal motility impairs esophageal acid clearance and therefore facilitates the development of mucosal damage in the esophagus, in other studies, no difference was observed in terms of mucosal damage in the esophagus between those with normal or abnormal motility in patients with pathological acid reflux (2, 16, 17). In our study, although we detected reflux in the pH meter in most of the patients, only 21.8% of them had mucosal damage endoscopically.

NEMD is associated with disturbances in the conduction of contractions in the esophageal body and relaxation in the lower esophageal sphincter (1, 2, 18). Müller M et al. (1) reported non-peristaltic contractions in more than half of the patients, prolonged contractions in 22.4%, low-amplitude contractions in 15%, and incomplete LES relaxation in 15.8% of the patients with NEMD. In our study, we found low-amplitude contractions in more than half of the patients, non-peristaltic contractions in 28.6%, and incomplete LES relaxation in 20.2%.

Manometry of the patients diagnosed with NEMD because they do not meet the diagnostic criteria for other primary esophageal motor diseases was repeated due to the continuation or increase of their complaints; 18 of these patients were diagnosed with achalasia, 5 with nutcracker esophagus, and 4 with DES. Müller et al. (1) diagnosed 53.6% of the patients with achalasia as a result of manometry repetitions in the four-year follow-up of the patients with NEMD. In another study, 23% of patients reported progression to achalasia and 14% to DES. (19, 20, 21).In another study, progression to nutcracker esophagus was reported in 14.3% of patients. (8). Unlike our study, these studies reported higher rates. This may be due to the manometry catheter being studied and the different patient populations. In our study, manometry was not performed again on all patients who were initially diagnosed with NEMD during their follow-up, but only on patients who had complaints and applied to us, thus our lower rates. In addition, we found esophageal dysmotility secondary to reflux in the majority of our patients.

The limitations of this study were that the changes in the complaints and motility of the patients could not be evaluated in the long-term follow-up because the study was retrospective, and endoscopy and 24-hour Ph-meter measurement were not performed in all patients. Although our unit is one of the largest motility laboratories in our country, conventional manometric methods are still used for reasons not caused by us. Although the manometry we used had superior Dentsleeve than other conventional manometry, high resolution manometry was not used. We could not performed detailed symptom evaluation because the patients were recorded only to have dysphagia and reflux symptoms in their initial complaints.

CONCLUSION

Patients with NEMD usually admit to the clinic with symptoms of dysphagia or reflux. It should not be forgotten that the majority of patients with NEMD are associated with reflux. Patients with NEMD who do not have endoscopic and radiological organic disorders should be re-evaluated with manometry and, if necessary, with further examinations if their complaints increase.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Bilkent City Hospital No:2 Clinical Researches Ethics Committee (Date: 01.03.2023, Decision No: E2-23-3579).

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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Evaluation of early readmissions following laparoscopic cholecystectomy

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ABSTRACT

Aim: The aim of our study was to evaluate the causes of 30-day hospital readmissions after laparoscopic cholecystectomy.

Material and Method: This study evaluated patients who underwent laparoscopic cholecystectomy (LC) between September 2011 and April 2019 and were admitted to the hospital within 30 days after discharge for follow-up and treated in the general surgery clinic.

Results: The study included 6,857 patients who underwent LC with a readmission rate of 2.1%. Of the patients, 34.7% were hospitalized for gastrointestinal complications, 33 (22.9%) for intraabdominal infections and bilomas, and 24 (16.7%) for bile duct complications. The most common bile duct problem was bile duct stones (9%).

Conclusion: Readmissions after cholecystectomy should be evaluated in detail, and necessary interventions should be undertaken in the short term.

Keywords: Laparoscopic cholecystectomy, readmission, complication, laparoscopy

INTRODUCTION

Advances in surgical and anesthetic techniques and changes in postoperative care have facilitated the safe discharge of patients following a one-day hospital stay after certain operations. One of the areas of development is laparoscopic surgery. Laparoscopy is now used very frequently in general surgery, and laparoscopic cholecystectomy (LC) has become the gold standard in the surgical treatment of gallbladder diseases (1). As a minimally invasive method, LC presents advantages such as early discharge from the hospital and early return to work. However, readmission due to postoperative complications causes morbidity and mortality, as well as an economic burden and a loss of workforce (2). This retrospective analysis was conducted to investigate the causes of early hospitalization after LC.

MATERIAL AND METHOD

Trial Design

This study was conducted retrospectively in the Department of Surgery, University of Health Science Konya City Hospital. The study protocol was approved by the Health Sciences University Hamidiye Scientific Researches Ethics Committee (Date: 26.03.2021, Decision No:11/17).

Patients who underwent LC between September 2011 and April 2019 and were admitted to the hospital within 30 days after discharge for follow-up and treatment in the general surgery clinic were evaluated. The classical four-port technique (two 10-mm and two 5-mm ports) was used in the surgery of all patients. The "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) criteria were utilized to develop the study protocol (3). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Participants and Eligibility Criteria

Inclusion criteria: Being 18 years or older, having undergone LC surgery, having a complaint associated with this procedure within 30 days of discharge, and being readmitted to the hospital again for a duration of 24 hours or more.

Exclusion criteria: Age under 18 years, laparoscopic surgery being converted to open surgery, the presence of gallbladder tumors, the use of anticoagulants, the use of a single port or incomplete or excess ports during surgery, and incomplete clinical data.

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Data Collection

Data were collected by reviewing the patient files and electronic hospital records of the patients included in the study. For the patients included in the study, demographic data, time elapsed from discharge to readmission, whether LC was performed under emergency or elective conditions, admission complaints, diagnostic methods, diagnoses, and comorbidities were recorded. Hypertension, diabetes mellitus, heart failure, chronic obstructive pulmonary disease/asthma, chronic steroid use, bleeding disorders, and chronic renal failure requiring dialysis were accepted as comorbidities. The length of hospital stay and treatment results were also evaluated.

Statistical Analysis

Statistical analyses were undertaken using SPSS 22.0 software (IBM Inc. Rochester, MN, USA). Quantitative variables were expressed as mean, standard deviation, percentage, median, minimum, and maximum values, and qualitative variables as rates.

RESULTS

Of the 6,857 patients who underwent LC, 144 were readmitted to the hospital in the early period for treatment. The rate of early readmission was 2.1%. The demographic characteristics and comorbidities of the patients are given in **Table 1**. Of the patients, 101 (70.1%) were female and 43 (29.9%) were male. The mean age of the patients was 51.9±15 years. There was no comorbidity in 86 (59.7%) of the patients, while 30 (20.8%) had multiple comorbidities and 28 (19.4%) had a single comorbidity. The most common comorbidities were hypertension and lung disease, followed by diabetes (**Table 1**).

Table 1. Comorbidities of the patients included in the study

Comorbidity	Number	Percentage
Lung disease	8	5.6%
Hypertension	8	5.6%
Diabetes	6	4.2%
Obesity	3	2.1%
Chronic renal failure requiring dialysis	1	0.7%
Smoking	2	1.4%
More than two comorbidities	30	20.8%
None	86	59.7%

Data are presented frequency and percent

LC was performed under emergency conditions in 34 (23.6%) of the patients and elective conditions in 110 (76.4%). The preoperative diagnosis leading to surgery was acute biliary cholecystitis in 34 (23.6%) of the cases, chronic biliary cholecystitis in 62 (43.1%), gallstones without cholecystitis in 43 (29.9%), biliary pancreatitis in four (2.8%), and chronic non-biliary cholecystitis in one.

In the first hospitalization of the patients, the mean length of hospital stay was 4±3.1 days. It was determined that 125 (86.8%) of the patients were discharged within one week after surgery, while 19 (13.2%) were hospitalized for longer than one week. Of these, six were hospitalized for more than one week due to an intra-abdominal abscess, 5 biliary tract injuries, 2 ileus, 2 biliary pancreatitis, 2 choledocholithiasis, 1 acute renal failure, and 1 surgical site infection. The number of patients discharged after one day was 63 (43.8%). The patients were readmitted to the hospital within an average of 6.1±5.8 days after their first discharge. For the second hospitalization, the mean length of hospital stay was 4.1±2.8 days, with 122 (86.5%) of the patients being discharged within one week and 19 (13.5%) being hospitalized for longer than one week.

The most common reason for hospital readmission was abdominal pain (n=86, 59.7%), followed by nausea and vomiting (n=22, 15.3%) (**Figure 1**). Surgical complications were present in 93.8% of the patients and non-surgical complications in 6.3%. Four patients were treated surgically, 21 with endoscopic retrograde cholangiopancreatography (ERCP), 34 with percutaneous drainage, and the remaining patients with medical therapy.

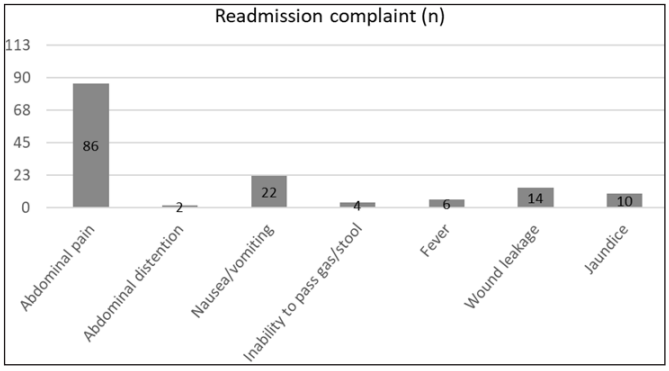

Figure 1. Readmission complaints of the patients

Bile duct complications were detected in 24 (16.7%) patients, with the most common being choledocholithiasis. Twenty-one of these patients were treated with ERCP (**Table 2**). In one patient with a bile duct injury, a percutaneous drainage catheter was inserted, and the patient was followed up with a controlled fistula that regressed during follow-up. In a patient with Strasberg Type A injury, the bile duct was repaired primarily. In the last patient, a bile leak occurred from the duct of Luschka, which was treated laparoscopically. Both patients who underwent surgery during their second hospitalization were discharged without any problems. Jaundice was the presenting complaint of six (25%) patients with bile duct complications.

In the diagnostic procedures of patients hospitalized with intraabdominal infections and bilomas, a percutaneous drainage catheter was routinely used under ultrasonography

Table 2. Diagnoses and treatments of the readmitted patients

Diagnosis	Number of patients n (%)	Treatment applied	Length of hospital stay, mean days (min-max)
GIS complications	50 (34.7%)	Medical therapy	2.7 (1-9)
Intraabdominal infections and bilomas	33 (22.9%)	Percutaneous drainage	4.8 (1-13)
Bile duct complications			5.5 (1-16)
Bile duct stones	13 (9%)	ERCP, stone extraction	
Bile duct injury and bile leak	6 (4.2%)	Surgery (n=2)	
		ERCP, biliary stenting (n=3)	
		Percutaneous drainage (n=1)	
Bile duct stenosis	5 (3.5%)	ERCP, biliary stenting	
Pancreatitis	13 (9%)	Medical therapy	4.9 (2-9)
Surgical site infections	13 (9%)	Wound care, medical therapy	3.8 (1-9)
Bleeding complications	2 (1.4%)	Medical therapy	2 (2-2)
Incarcerated trocar site hernias	2 (1.4%)	Surgery	7 (4-10)
Respiratory complications	3 (2.1%)	Medical therapy	2 (2-2)
Urinary complications	3 (2.1%)	Medical therapy	5.6 (2-8)
Neurogenic complications	1 (0.7%)	Medical therapy	8

Data are presented frequency (percent) or mean (min-max), GIS: gastrointestinal system; ERCP: endoscopic retrograde cholangiopancreatography

guidance. A Richter hernia was seen in one of the two patients with trocar site hernias, and segmental small bowel resection was performed. The other patient had omental herniation and underwent herniorrhaphy. Both patients had multiple comorbidities. Mortality occurred in a total of three patients, of whom two had bile duct complications and one had respiratory complications.

In the study group, 81 (56.2%) of the patients were hospitalized for more than one postoperative day, whereas 63 (43.8%) were admitted for one day. Table 3 presents the clinical characteristics of patients according to whether they were discharged on the first postoperative day. There was no statistically significant difference between age, gender, preoperative diagnosis, ASA scores, readmission diagnosis, and pathologic diagnosis between those discharged on the first day and those with longer hospitalization.

DISCUSSION

In this study, we aimed to develop foresight to evaluate the possible early complications of LC and prepare an action plan accordingly. With the developing technologies and increasing experience of surgeons, LC operations can be performed very successfully, and patients can be discharged without any problems. Although it is predicted that patients will have completely recovered at the time of discharge, readmissions may occur due to undesirable complications or complaints in the early postoperative period. In the current study, the rate of readmissions after LC was found to be 2.1%. In a meta-analysis of McIntyre et al. (4) evaluating 52,628 readmissions among 1,573,715 LC cases, the overall readmission rate was reported to be 3.3% (range, 0.0-11.7). Thus, the rate of readmission in our study was lower than that reported in the literature.

Currently, LC is used as the first treatment option in the surgical treatment of gallbladder diseases across the world, with up to 92% of cholecystectomies being performed laparoscopically (5). In a study by Rosero et al. (6), surgical complications, postoperative pain, infections, postoperative nausea, and vomiting constituted 61% of readmission diagnoses. In the same study, it was observed that resurgery was required at a rate of 0.06% after LC (6). In our cohort, the rate of surgical complications was low, which supports the literature. In addition, 59% of the patients requiring readmission improved with medical therapy, confirming that LC is an ideal treatment procedure in terms of both complications and patient comfort.

It has been reported that 74% of surgical patients still experience moderate/extreme pain after discharge. Despite clinical advances in pain management, there appears to be little progress in pain management following surgery (7). It is common for LC patients to be discharged the day after surgery. However, postoperative abdominal pain remains the most common cause of readmission, and most patients are hospitalized again for only one day for observation purposes (2). Similar to the literature, in our study, 43.8% of the patients were discharged on the day after LC, 59.7% of the patients were readmitted to the hospital with abdominal pain, and 43.8% of these patients were followed up in the hospital for at least one day. Although it remains controversial whether certain types of surgery are associated with a higher incidence of nausea and vomiting, both the laparoscopic approach and the cholecystectomy procedure have been reported as risk factors for postoperative nausea/vomiting (8).

In this study, 56.2% (n=81) of those who were readmitted to the hospital were hospitalized for more than 1 day after surgery. However, when clinical features were compared according to whether or not there was hospitalization for

Table 3. Clinical features according to discharge on the first postoperative day

Items	Discharged on the first day 63 (43.8%)	Not discharged on the first day 81 (56.2%)	p
Under 65 years	82.6%	72.8%	0.51
Female sex	71.4%	69.1%	0.77
Preoperative diagnosis			0.13
Acute gallstone cholecystitis	19%	27.2%	
Chronic gallstone cholecystitis	81%	72.8%	
ASA score			0.07
1	38.1%	25.9%	
2	38.1%	40.7%	
3	23.8%	25.9%	
4		7.4%	
Readmission diagnosis			0.28
Ileus	30.2%	38.3%	
Bile duct complications	12.7%	19.8%	
Intraabdominal infection	28.6%	18.5%	
Surgical site infection	6.3%	8.6%	
Bleeding	1.6%	1.2%	
Respiratory complications	3.2%	1.2%	
Other	17.4%	12.4%	
Pathologic diagnosis			0.50
Acute gallstone cholecystitis	12.7%	13.6%	
Chronic gallstone cholecystitis	84.1%	80.2%	
Gangrenous cholecystitis	1.6%	1.2%	
Malignancy	-	1.2%	
Xanthogranulomatous cholecystitis	1.6%	1.2%	
Erosive cholecystitis	-	1.2%	
Biliary cystadenoma	-	1.2%	

Data are presented frequency or percent

more than one postoperative day, there was no significant difference (**Table 3**).

As in every surgical procedure, gastrointestinal system (GIS) complaints are also naturally observed in patients after cholecystectomy and may even be severe enough to require hospitalization. GIS symptoms are expected to be seen even more frequently following surgery performed on the gallbladder compared to other operations. In the current study, a high rate of patients had severe GIS complaints requiring hospitalization; however, most of these symptoms improved with medical therapy. Therefore, we consider that physicians should favor drug treatments for GIS symptoms at the time of discharge to reduce the rate of readmission.

In the literature, the incidence of bile duct injuries is reported to be 0.4% in LC and 0.2% in open cholecystectomy (9). Although LC is regarded as the gold standard, bile duct injuries, which are less likely to occur in open surgery, are more prevalent in LC and can lead to bile duct problems later. Surgeons need to anticipate this during the postoperative discharge. Considering the high incidence of bile duct complications after LC in our study, it would be appropriate to call the patients for a control in the early period after discharge, evaluate whether there is any bile duct injury, and perform necessary investigations accordingly.

In a study by Rosero et al. (6), it was reported that 63.6% of the patients who presented to the hospital with surgical complications had bile duct obstruction, which was noted to be the most common diagnosis at readmission. In our study, readmission due to bile duct complications was seen at a rate of 16.7%. While the rate of all bile duct complications related to LC is 0.4-0.6% in the literature, it was found to be 0.35% in our study (9-13). Bile duct injuries were present in two of the three patients who died. Two of the patients readmitted to the hospital with bile duct complications died during their hospital stay. Bile duct complications were examined under three main headings: bile duct stones, bile duct injuries/bile leakage, and biliary stenosis. Ultrasonography or magnetic resonance cholangiopancreatography was used in the diagnosis of these patients, and sphincterotomy, stone extraction, and stent insertion were performed using ERCP in their treatment. One of the patients with bile duct injuries was followed up and treated with a controlled fistula by inserting a percutaneous catheter. We consider that a detailed examination should be conducted to diagnose bile duct complications, and the diagnosis and treatment processes should not be delayed due to the possibility of their fatal progression.

Most of our patients (66.7%) who were readmitted to the hospital with the complaint of fever were diagnosed with intraabdominal infections or bilomas. Interventional procedures were performed on these patients. Therefore, we consider that patients who have undergone LC should not be neglected in the early period after discharge and should be evaluated in detail in terms of complications of bile duct injuries, bilomas, and abscesses. This can prevent delays in interventions and longer hospitalizations due to possible complications.

Pancreatitis often originates from biliary stones. However, due to the traction on the gallbladder during LC and manipulations for dissection in difficult cases, small stones may enter the bile duct. As a result, patients may suffer from pancreatitis after LC. In our study, pancreatitis developed in 9% of the patients within the first 30 days after LC, while this rate is reported to be 5.02% in the literature (2). Although all patients with acute pancreatitis in our series improved with medical therapy, some previous studies have reported the requirement of ERCP and even surgery (14). These patients presented with severe symptoms beyond expected postoperative

abdominal pain (**Figure 1**). Therefore, it would be appropriate to evaluate the current symptoms of patients in terms of acute pancreatitis during early follow-up.

Another aspect that is often overlooked in LC is the possibility of trocar site hernia development. Trocar site hernias are late complications commonly seen after LC. Based on the results of our study, we recommend that surgeons pay attention to these complications and take the necessary precautions during surgery, since they can also require emergency surgical treatment in the early period.

In a study by Moghadamyeghaneh et al. (2), the 30-day mortality rate of 3,315 hospitalized patients was found to be 1.4%. In our study, mortality occurred in three (2.1%) of the 144 patients. Two of these patients died due to bile duct injuries and related complications after LC, and one patient due to respiratory complications. Therefore, bile duct injuries can be considered the most alarming complications after LC, and especially undetected bile duct injuries may be the most important cause of mortality.

Limitations

We were not able to obtain data on the duration of surgery, whether the gallbladder was perforated, or the number of cholecystitis attacks before surgery.

CONCLUSION

Complications that may develop after LC can result in severe morbidity and even mortality. Readmission to the hospital after cholecystectomy should be evaluated in detail, and necessary procedures should be undertaken in a short time. If necessary, patients should be hospitalized and followed up. As described in the literature, bile duct complications were also prominent in our study and resulted in the highest morbidity and mortality in our cohort; therefore, they should be prioritized in the evaluation of readmitted cases. The close monitoring of patients' ongoing abdominal pain, nausea, and vomiting symptoms before discharge and the investigation of the etiology of these symptoms if they do not resolve can prevent readmission after discharge and allow for the detection of complications earlier.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Health Sciences University Hamidiye Scientific Researches Ethics Committee (Date: 26.03.2021, Decision No:11/17).

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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Is neutrophil lymphocyte ratio magic or not?

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ABSTRACT

Aim: To evaluate the predictive value of preoperative ratio of neutrophils to lymphocytes (NLR) in distinguishing between benign and malignant masses, as inflammation plays a significant role in the development and emergence of cancer.

Material and Method: This retrospective study included 155 patients who underwent surgery due to an adnexal mass between December 2020 and December 2021 (55 were malignant, 100 were benign). Age, parity, tumor stage, chemotherapy, CA 125, CRP, neutrophils, lymphocytes, NLR, were recorded. The Mann-Whitney, the Chi-square test and multiple linear regression were used. The cut-off values of the variables were determined by calculating the areas under the receiver operating characteristic curve (ROC) for the purposes of differential diagnosis in the presence of malignancy, and by analyzing the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood-ratio (LR) (+) values. A P-value of <0.05 was established as the significance level.

Results: Malignant tumors showed higher values of neutrophils, CA 125, CRP, and NLR (p=0.018, p=0.0001, p=0.001, p=0.01, respectively), whereas benign group showed higher values of lymphocytes (p=0.011). At cut-off> 2.79 for NLR; sensitivity was found to be 59.36%, specificity 75.51%, positive predictive value (PPV) 58.44, negative predictive value 75.58, LR (+) value 2.3. At cut-off> 36.9 for CA-125; sensitivity was 80.00%, specificity was 78.63%, positive predictive value was 67.72%, negative predictive value was 87.53%, LR (+) value was 3.73.

Conclusion: The primary outcome of our study is that the likelihood of malignancy in a patient with an NLR value of>2.79 is 2.3 times higher than in a patient with an NLR value of <2.79 in distinguishing between benign and malignant adnexal masses. The secondary outcome is that the likelihood of malignancy in a patient with a CA-125 value of>36.9 is 3.73 times higher than in a patient with a CA-125 value of <36.9.

Keywords: NLR, CA-125, ovarian cancer

INTRODUCTION

Epithelial ovarian cancer (EOC) accounts for approximately 90% of ovarian cancer cases and approximately 75-80% are diagnosed at an advanced stage (1). Despite the innovations in cancer treatment in the last decade, more than two-thirds of EOC cases are diagnosed at an advanced stage, and the 5-year survival rate for advanced stage (stage 3-4) ovarian cancers is 25% (2). The prognosis of EOC is poor due to the absence of specific symptoms in the early stage and its ability to rapidly metastasize.

The relationship between inflammation and cancer has been the subject of many studies in recent years, especially in ovarian cancers, and with the widespread use of tumor markers, other parameters related to prognosis have become the focus of attention. Recent findings have expanded the understanding that inflammation plays a crucial role in tumor progression. It's becoming evident that the tumor microenvironment, primarily controlled by inflammatory cells, is a vital component in the development of cancer, promoting growth, survival, and spread (3). The ratio of neutrophils to lymphocytes (NLR) in peripheral blood is a general indicator of inflammation and oxidative stress and reflects the balance of the inflammatory and immune systems, serving as a useful predictor of cancer prognosis by indicating the balance between pro-tumor and anti-tumor status (4). Neutrophil/Lymphocyte ratio may play a role in the prognosis of many benign and malignant diseases (5). These

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markers can be acquired from a routine blood test, which is known to be cost-effective, reproducible, less invasive, and currently the universally accepted test. Past studies have also cited that these inflammatory markers could distinguish benign ovarian masses and ovarian cancers (6). However, the cut-off value still remains unclear. (7). Our aim in this study is to evaluate the predictive value of preoperative NLR in the differentiation of benign and malignant masses.

MATERIAL AND METHOD

The study was carried out with the permission of İstanbul City Hospital Clinical Researches Ethics Committee (Date: 02.11.2022, Decision No: 334). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study included 155 patients who underwent surgery due to adnexal mass in our clinic between December 2020 and December 2021. Patients who received any radiation therapy or chemotherapy prior to surgical exploration were excluded, as well as patients with accompanying autoimmune diseases or evidence of active infection. The diagnoses of the patients included in the study were confirmed by pathological evaluation. The staging of adnexal masses was based on surgical findings and FIGO criteria (2014), while their histological types were identified via WHO system (2003). Pathological diagnosis was divided into benign masses (e.g. serous cystadenoma, mucinous cystadenoma, mature teratoma) and epithelial ovarian cancer (e.g. serous, mucinous, endometrioid and other epithelial ovarian cancer). Demographic and clinicopathological data of patients with adnexal masses were analyzed and documented, including preoperative complete blood count values. Blood cell counts were obtained from a preoperative routine blood test conducted within a week prior to the operation. After debulking surgery in the malignant group, patients began the first cycle of platinum-based combination chemotherapy, which is repeated every 3 weeks for 6 cycles. Routine abdominal and pelvic CT scans were performed after the first three cycles of chemotherapy and after completion of the first-line treatment of six cycles. According to the chemotherapy response, the groups divided into platinum-sensitive and platinum-resistant groups were compared in terms of NLR, CRP, and CA 125.

Statistical Analysis

In this study, statistical analyses were conducted using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

In evaluating the data, descriptive statistical methods (mean, standard deviation, median, interquartile range) were used, as well as the Shapiro-Wilk normality test to examine the distribution of variables. For variables showing normal distribution, the independent t-test was used for comparison of two groups, and the Mann-Whitney U test was used for variables not showing normal distribution. The chi-square test was used for comparison of qualitative data. Logistic Regression analysis was performed to determine the factors affecting the presence of malignancy. The area under the ROC curve was calculated for discriminative diagnosis of malignancy presence, and cut-off values were determined for variables based on sensitivity, specificity, positive predictive value, negative predictive value, and LR (+) values. Results were evaluated at a significance level of $p<0.05$.

RESULTS

The average age of patients in the malignant group was 53.25±10.96, higher than the average age in the benign group which was 43.74±14.44 (p=0.0001). No statistically significant difference was observed between the average gravida and parity of the benign and malignant groups (p=0.216, p=0.170). The presence of multicystic tumors in malignant adnexal masses was found to be statistically significantly higher than in the benign group (p=0.0001). The presence of septation in tumors in the malignant group was found to be statistically significantly higher than in the benign group (p=0.0001). The presence of bilaterality in tumors in the malignant group was found to be statistically significantly higher than in the benign group (p=0.029). No statistically significant difference was observed between the average diameters (cm) of the benign and malignant groups (p=0.102). The average neutrophil levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.018). The average lymphocyte levels in the malignant group were found to be statistically significantly lower than in the benign group (p=0.011). The average CRP levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.001). The average CA-125 levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.0001). The average NLR levels in the malignant group were found to be statistically significantly higher than in the benign group (p=0.01). The data is summarized in **Table 1**.

Table 1. Baseline patient characteristics

		Benign n:100		Malignant n:55		P
Age	Mean ± SD	43,74±14,44		43,74±14,44		0,0001*
Parity	Median (IQR)	2 (1-3)		2 (1-4)		
Loculus						0,0001
Unilocular		68	68.00%	4	7.27%	
Multilocular		32	32.00%	51	92.73%	
Septation						0.0001
Absent		77	77.00%	7	12.73%	
Present		23	23.00%	48	87.27%	
Laterality						0.029+
Unilateral		92	92.00%	44	80.00%	
Bilateral		8	8.00%	11	20.00%	
Diameter (cm)	Mean ± SD	9.57±5.65		11.68±7.64		0.102‡
Neutrophil	Mean ± SD	4.75±1.55		5.85±3.23		0.018‡
Lymphocyte	Mean ± SD	2.17±0.69		1.91±0.67		0.011‡
CRP						0.001‡
Mean ± SD		8.87±16.50		32.44±45.93		
Median (IQR)		4.50 (1.4-7.82)		10.88 (2.53-53.73)		
CA-125	Mean ± SD	33.71±5032		494.7±894.99		0.0001‡
NLR	Mean ± SD	2.39±1.11		3.46±2.30		0.001‡

*Independent t-test ‡ Mann-Whitney U-test + Chi-Square test

A Multivariate (Multiple) Regression analysis was performed to determine the factors affecting the presence of malignancy using the variables of age, septation, bilateral, neutrophil, lymphocyte, CRP, CA-125 and NLR. The variables of age (p=0.06), septation (p=0.102), bilateral (p=0.221), neutrophil (p=0.679), lymphocyte (p=0.539), CRP (p=0.192) and NLR (p=0.067) were found to be insignificant while CA-125 (p=0.017) was found to be statistically significant. The results are summarized in **Table 2**.

Table 2. Multivariate (Multiple) Regression analysis for the factors affecting the presence of malignancy using the variables

	Multiple Regression Analysis		Adjusted Multiple Regression Analysis‡	
	OR %95CI	P	OR % 95CI	P
Age	1.04 (1.00-1.09)	0.06	-	-
Multilocular	0.19 (0.03-1.23)	0.082	0.98 (0.94-1.01)	0.232
Septation	0.25 (0.05-1.32)	0.102	0.97 (0.94-1.03)	0.071
Bilateral	0.34 (0.06-1.93)	0.221	0.98 (0.95-1.01)	0.228
Neutrophil	0.85 (0.40-1.81)	0.679	0.99 (0.98-1.04)	0.302
Lymphocyte	1.35 (0.32-5.81)	0.539	1.03 (1.00-1.05)	0.056
CRP	1.01 (0.99-1.04)	0.192	1.03 (0.98-1.11)	0.191
CA-125	1.01 (1.00-1.02)	0.017	1.07 (1.00-1.15)	0.013
NLR	1.52 (0.56-4.17)	0.067	1.02 (0.99-1.04)	0.172

The area under the ROC curve for Neutrophil in the differential diagnosis of malignancy was found to be 0.615 (0.533-0.692), for Lymphocyte 0.625 (0.543-0.702), for CRP 0.663 (0.583-0.738), which are below the desired value of 0.700. The area under the ROC curve for NLR was 0.702 (0.602-0.759), and for CA-125 it was 0.835 (0.766-0.890), which is above the desired value of 0.700. The results are summarized in **Table 3**.

Table 3. The area under the ROC curve

	AUC	SE	95% CI
Neutrophil	0.615	0.048	0.533- 0.692
Lymphocyte	0.625	0.046	0.543- 0.702
NLR	0.702	0.046	0.602- 0.759
CRP	0.663	0.047	0.583- 0.738
CA-125	0.835	0.037	0.766- 0.890

At cut-off >2.79 for NLR; sensitivity was found to be 59.36%, specificity 75.51%, positive predictive value (PPV) 58.44, negative predictive value 75.58, LR (+) value 2.3. At cut-off >9.87 for CRP; sensitivity was found to be 54.55%, specificity 78.57%, positive predictive value (PPV) 58.80%, negative predictive value 75.54%, LR (+) value 2.15. At cut-off >36.9 for CA-125; sensitivity was 80.00%, specificity was 78.63%, positive predictive value was 67.72%, negative predictive value was 87.53%, LR (+) value was 3.73. The results are summarized in **Table 4**.

Table 4. Cut-off value for NLR, CRP, CA- 125

	Cut off	Sensitivity	Specificity	PPV	NPV	LR (+)
NLR	>2.79	59.36	75.51	58.44	75.58	2.30
CRP	>9.87	54.55	78.57	58.80	75.54	2.15
CA-125	>36.9	80.00	78.63	67.72	87.53	3.73

As a factor affecting the presence of malignancy, Logistic Regression analysis was performed for the NLR value >2.79, and the presence of NLR >2.79 was found to be 3.6 (1.79-7.23) times more effective on the malignancy (p=0.0001). When corrected for NRL >2.79, a high level of NRL was found to be 1.03 (1.79-7.23) times effective on malignancy (p=0.0001). The results are summarized in **Table 5**.

Table 5. Logistic Regression analysis for the NLR value

	Multiple Regression Analysis		Adjusted Multiple Regression Analysis‡	
	OR 95% CI	P	OR 95% CI	P
NLR >2,79	3.6 (1.79-7.23)	0.0001	1.03 (1.01-1.04)	0.0001

No statistically significant differences were observed between the average ages of the chemotherapy (CT) sensitive and resistant groups (p=0.377). No statistically significant differences were observed between the average CRP levels of the CT sensitive and resistant groups (p=0.511). No statistically significant differences were observed between the average CA-125 levels of the CT sensitive and resistant groups (p=0.753). No statistically significant differences were observed between the average NLR levels of the CT sensitive and resistant groups (p=0.739).

DISCUSSION

The presence of inflammation can lead to the growth and spread of various types of cancer. During inflammation, there is often a deregulation in the signaling pathways within cells, leading to genetic instability, DNA damage, and increased cell growth and blood vessel formation, all of which contribute to the transformation into malignancy. The ability of NLR to serve as a prognostic factor is largely due to its ability to indicate the infiltration of neutrophils and lymphocytes. Cancer cells also release substances that trigger a systemic inflammatory response, leading to the accumulation of neutrophils which can stimulate cancer progression by secreting interleukins (IL-2, IL-6, IL-10) and cytokines such as tumor necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF) (8). VEGF, a proangiogenic factor, plays a role in cancer development by promoting angiogenesis. Additionally, high levels of TNF-α and IL-10 can lead to a decrease in lymphocyte count and dysfunction. Furthermore, elevated neutrophils can also stimulate the production of the angiogenesis cytokine VEGF, thereby further fueling cancer growth (9). The depletion of lymphocytes is commonly recognized as a manifestation of a weakened T-lymphocyte-mediated antitumor response, which is considered a negative prognostic factor. The ratio of elevated neutrophils to decreased lymphocytes can be a useful marker of systemic inflammation and patient outcome, and thus NLR has the potential to serve as a prognostic indicator to some extent. The preoperative NLR ratio has been studied as a subject for many types of cancer (10,11). Despite publications linking elevated NLR values with poor prognosis, the results are inconsistent. For example, studies on breast cancer patients have not found a relationship between NLR and prognostic value (12). In our study, the area under the ROC curve for NLR was found to be 0.702 (0.602-0.759), which is above the desired 0.700, and for CA-125 the area under the ROC curve was 0.835 (0.766-0.890). In our study, Logistic Regression analysis was performed and NLR values higher than>2.79 were found to be 3.6 (1.79-7.23) times effective on malignancy (p=0.0001). For CA-125, a cut-off value of>36.9 was found with a sensitivity of 80.00%, specificity of 78.63%, positive predictive value of 67.72%, negative predictive value of 87.53% and LR (+) value of 3.73. In another similar study, NLR and CA 125 were found to be potential diagnostic factors for ovarian cancer. A this study indicated that when predicting ovarian cancer, the area under the curve (AUC) was 0.95 for log (CA125) (95% CI, 0.91-0.98; sensitivity was 81.3%; specificity was 96.3%), and 0.92 for the NLR (95% CI, 0.86-0.98; sensitivity was 92.6%; specificity was 79.2%) (13). A meta-analysis conducted found that preoperative CA 125 is a reliable tool for predicting progression of EOC, in parallel to our study (14).

Studies linking the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) to the response to and prognosis of ovarian cancer patients treated with platinum-based chemotherapy exist. In this study, the results showed that the AUC, sensitivity, and specificity of an NLR> 3.02 for predicting platinum resistance were 0.819, 75.0%, and 81.45%, respectively (15). In our study, no statistically significant difference was observed between the average NLRs of the CT sensitive and resistant groups (p=0.739). There have been numerous studies regarding the ability of NLR to predict progression-free survival (PFS) and overall survival (OS) in ovarian cancer patients. For example, a meta-analysis found that a high NLR (cut-off: 3.3, p=0.03) was associated with shorter progression-free survival (PFS) and overall survival (OS) (16). Our study did not evaluate PFS and OS because the follow-up time of patients was short, which is one of the limitations of our study.

The use of NLR and other inflammatory markers, in addition to potential tumor markers, is hopeful in patients who present with adnexal mass. NLR can serve as an easily accessible and cost-effective prognostic marker for EOC in clinical practice. However, the interpretation of this finding requires prospective studies with large patient populations and longer follow-up assessments due to high heterogeneity.

CONCLUSION

Our primary outcome shows that the likelihood of malignancy in a patient with NLR value of >2.79 is 2.3 times higher than that in a patient with NLR value of <2.79 in the distinction of benign and malignant adnexal masses.

The secondary outcome shows that the likelihood of malignancy in a patient with a CA-125 value of >36.9 is 3.73 times higher than that in a patient with a CA-125 value of <36.9.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul City Hospital Clinical Researches Ethics Committee (Date: 02.11.2022, Decision No: 334).

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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The impacts of Kinesio taping on muscular fatigue and proprioception following fatigue among adolescent basketball players

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ABSTRACT

Aim: The present study attempted to investigate the impacts of Kinesio taping on proprioceptive responses of the knee joint before and after muscular fatigue.

Material and Method: Thirteen healthy basketball players were recruited for this study. A fatigue protocol was designed with a load of 70% of the maximum quadriceps muscle strength and applied to the dominant lower extremity, including repetitive knee flexion and extension in a sitting position between 0°-90°. Fatigue was assessed using the Borg scale. The protocol was administered to the same participants twice at a one-week interval. Proprioception in the knee joint was assessed using the angle reconstruction test. In the evaluation of proprioception, the target angle was set as 45° of knee flexion and was measured with a digital goniometer. In the second-week measurements, the same protocol was repeated immediately following Kinesio tape application to the quadriceps femoris muscle with the facilitation technique.

Results: The findings revealed no significant within-group differences between the proprioception measurements before and after fatigue ($p > 0.05$). It was also the case in the evaluation with Kinesio taping ($p > 0.005$). However, the number of movement repetitions significantly differed between the groups in the fatigue protocol ($p < 0.05$).

Conclusion: The proprioception values of pre- and post-fatigue did not significantly differ when Kinesio taping was applied. Overall, it was concluded that Kinesio taping was an effective factor in reducing fatigue and contributed to endurance by delaying the onset of fatigue.

Keywords: Adolescent, quadriceps muscle, athletic tape, proprioception, basketball

INTRODUCTION

Kinesio taping (KT) is a method that has grabbed substantial attention substantial attention for its widespread use as a therapeutic tool in physiotherapy and rehabilitation in recent years. Tapes are widely used in clinical practice. While having a thickness similar to the epidermis layer of the skin, they bear flexibility overlapping with the elastic properties of human skin (1-3). To accomplish a desirable result from the application, it is key to assess the patient to be treated well, to determine the ultimate purpose, to choose the appropriate region, and to apply the appropriate tension and angle to the region (4). KT techniques can be applied with I, Y, X, web, fan, or ring-shaped tapes (4). Although the impacts of KT on proprioception have not been fully elucidated (5-7), it is thought that KT may improve performance by enhancing proprioception (8). The ability to sense the location or movement of the body or body part in space is called proprioception (9).

Proprioception helps with the proper functioning of posture, balance, coordination, and joint stabilization (10). Many receptors (e.g., mechanoreceptors) can sense proprioception (11), and it is often proposed that there may be an increase in proprioception by stimulating mechanoreceptors with KT (8). It is thought that physical fatigue (e.g., muscular fatigue) adversely affects joint proprioception and impairs neuromuscular control. Although the literature hosts a plethora of studies investigating the changes within proprioception following fatigue, they have not been able to reveal what components in the proprioception pathway do not function adequately following fatigue (5,12,13). Generally it is accepted that local muscular effects arising from fatigue may have negative effects on proprioception (5). The present study aimed to have a contribution to the literature by focusing on

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this perspective by exploring the impacts of KT applied to the quadriceps femoris muscle with the facilitation technique on the proprioceptive sense during and after fatigue. The acute effect of KT is evaluated in this study. Because no consensus is available in the literature whether the KT application increases muscle strength in the acute phase following application, it is intended in this study to find out whether KT has (15-17).

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Medical Faculty Non interventional Clinical Researches Ethics Committee (Date: 26.06.2019, Decision No: 2019.06.18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The participants and their parents provided informed consent after receiving a brief explanation of the purpose and scope of the research. Thirteen healthy adolescent athletes from the An Kavra Sports Club were recruited for the study. Eligibility was confirmed by reviewing each participant's case report. The study included 13 adolescent healthy individuals who had been playing amateur basketball with the club for at least a year. Moreover, the participants were required not to develop an allergic reaction to 5 cm wide tape attached to their forearm area. The tape was kept on the arm for 10-15 minutes (17). Then, the participants' demographic characteristics such as age, height (cm), body weight (kg), and dominant side were noted down.

The inclusion criteria were set as follows: playing basketball, being an adolescent (10-19 years), having no history of lower extremity injury, and volunteering to participate in the study. Nevertheless, those with a history of lower extremity injury, fractures, and surgery history, neuromusculoskeletal disorders, and cardiovascular issues in the last six months were excluded from the study (14). When needed, the termination criteria were renouncing voluntary participation in the study and withdrawal from/not being able to fill out the data collection tool.

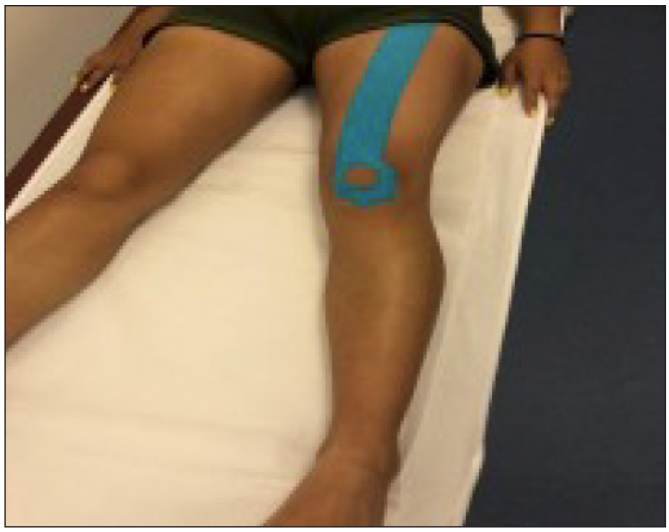
The present study aimed to investigate the impacts of fatigue in the quadriceps femoris muscle on the proprioception of the knee joint. Hence, a fatigue protocol was designed where one's quadriceps muscle needs to be exhausted till it can no longer move. This protocol was planned to be performed with a load of 70% of the maximum quadriceps muscle strength. It was planned to be carried out with a weight that was 70% of maximal isometric muscle strength of the quadricesp femoris muscle (**Picture 1**). To settle the protocol, each participant's quadriceps muscle strength during knee extension was first measured with a hand-held muscle strength dynamometer (Baseline Evaluation System, New York). To prepare the muscle for the measurement, the participants were recruited for five minutes of brisk walking and a short (3× 30 sec) stretching exercise on their quadriceps femoris muscle (18). Extension strength was measured in the sitting position with the hip and knee joints flexed to 90°. The test was performed isometrically, and the results were recorded in kg-force (19). The procedure was replicated three times, and the mean of the three measurements was recorded. The results also helped to confirm the participants' dominant side. The protocol was implemented by asking each participant to bring their knee from 90° flexion to full extension in the sitting position based on the pre-determined load. The protocol was repeated until each participant could no longer move their thigh, and the number of repetitions was recorded throughout the protocol (20).

Picture 1. Isometric quadriceps muscle strength measurement (A picture was taken by author)

This fatigue protocol was applied to same individuals twice with a one-week interval. In the first week, it was performed without KT and in the second week it was repeated by applying KT to the Quadriceps Femoris muscle with facilitation technique. The evaluation in the first week was assigned as control group, while the second evaluation was the study group and comparisons were made between them regarding fatigue and proprioception. The protocol was administered to the same participants twice at a one-week interval. The first-week protocol was performed without KT and marked as the control measurement (group). The second-week protocol,

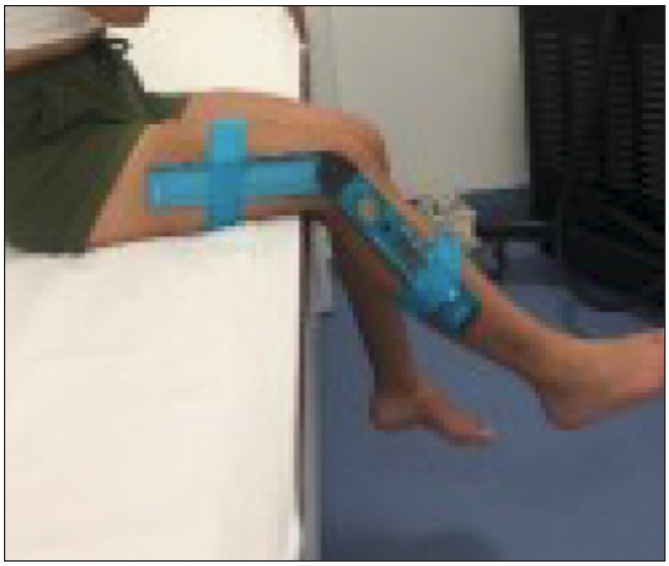
on the other hand, was administered with KT to the quadriceps muscle with the facilitation technique and considered the experimental measurement (group). The groups were then compared regarding fatigue and proprioception.

KT was performed using 5 cm wide standard tape. The tape was attached to the clean and moisture-free skin of the quadriceps femoris muscle with the facilitation technique from the origin to the insertion. After securing the anchor at the origin of the muscle, the quadriceps muscle was taken to its most tense position upon the knee joint with max flexion, and the I-shaped tape was attached to the patellar tendon without applying tension from the spina iliaca anterior superior (SIAS) (**Picture 2**).



Picture 2. Application of kinesio tape to the quadriceps muscle with facilitation technique (A picture was taken by author)

The joint position sense test (angle reconstruction test) was utilized to evaluate the proprioceptive sensation of the knee joint, and proprioception was evaluated using a digital goniometer (14). The test procedure was performed while participants were seated with bare legs. During the measurement, the participants' eyes and ears were closed. At a knee flexion angle of 90°, the goniometer was adjusted and fixed as the fixed arm was aligned with the thigh, the movable arm was aligned with the lateral malleolus, and the pivot point was the lateral femoral condyle. The target angle for proprioception measurement was set at 45° (**Picture 3**). First off, each participant was recruited for a demo to teach the target angle. The knee was passively brought to the target angle, the movement was stopped, and the participant was asked to concentrate for three seconds, and the knee was brought back to the starting position. The demo was performed actively and passively 3-7 days before the actual measurement until each participant grabbed the idea. The target angle was reminded to the participants during the first-week measurement, and they were asked to close their eyes and ears, find the target angle, and maintain that angle for three seconds. The test was repeated five times. Afterward, the values when they felt to accomplish the target angle were recorded in these trials, and the mean and error values were noted (5, 21-24). Measurements were taken in a quiet and ventilated environment to minimize distractions.



Picture 3. Evaluation of proprioception of the knee joints (A picture was taken by author)

The perceived level of fatigue during the tests was assessed using the modified Borg CR-10 scale (25, 26). Individuals were asked to rate the level of fatigue they felt between 0 (no fatigue) and 10 (motionless). The loading was maintained until the participants' perceived fatigue reached a score of 9 or 10 points (25). The protocol was terminated upon reaching such a score, and the proprioception values were remeasured and recorded.

Statiscal Analysis

Prior to this study, power analysis has been conducted. Comparison of pre- and post-fatigue was conducted via t-test. The effect size value, Cohen's d was 3.4 which was calculated based on the Absolute error (degree) of similar study (27). The outcome of this analysis conducted with 80% power and 5% error has revealed that the number of participants that required to be evaluated was 3. Therefore, 13 participants have been involved in this study. Descriptive statistics for quantitative variables were presented as mean±standard deviation and frequency (percentages) for qualitative variables. The paired samples t-test was used to compare the pre- and post-fatigue proprioception values. P-values of <0.05 was considered statistically significant.

RESULTS

The sample consisted of thirteen healthy athletes of An Kavra Sports Club, 2 (15.38%) females and 11 males (84.61%). The study was performed between January to April in 2019. While the dominant side of 12 (92.3%) participants was the right extremity, it was the left extremity in only one participant (7.7%). The participants had a mean age of 12.38 years (12-14 years), a mean height of 163.76 cm, a mean body weight of 53 kg, and a mean body mass index (BMI) of 21.05 kg/m². It was found that all participants attended secondary school, played basketball for more than a year, and had no history of lower extremity injury. **Table 1** presents the participants' physical and demographic characteristics.

Table 1. Participants' physical and demographic characteristics

Physical Characteristics	**Mean**
Age	12.38
Height (cm)	163.76
Weight (kg)	53
BMI (kg/m²)	21.05
Demographic Characteristics	**n (%)**
Sex	
Female	2 (15.38)
Male	11 (84.51)
Educational attainment	
Secondary school	13 (100.0)
High school	0 (0.0)
Dominant extremity	
Right	12 (92.3)
Left	1 (7.7)

First, the comparison of pre- and post-fatigue proprioception values at the target angle (45°) of knee flexion without KT yielded no significant differences between the mentioned values (p>0.05. Similarly, there was no significant difference between the pre- and post-fatigue proprioception values at the target angle of knee flexion with KT application (p>0.05; **Table 2**).

On the other hand, the pre-fatigue proprioception values at the target angle of knee flexion did not significantly differ between two weeks of the measurements (p>0.05). The findings also revealed no significant difference between the post-proprioception values at the target angle of knee flexion without KT and the mentioned values with KT in the second week (p>0.05; **Table 2**). The findings also demonstrated a significant difference between the number of movement repetitions during fatigue loading without KT in the first week and with KT in the second week (p<0.05; **Table 2**).

Table 2.

	Pre	**Post**	**Difference**	**p**
	Mean±SD	**Mean±SD**	**Mean±SD**	
First-week PV	45.19+3.22	43.13+6.35	2.06±5.41	0.195
Second-week PV	44.85+1.61	44.97+4.73	-0.12±4.42	0.923
First-week and second-week PRE-PV	45.19+3.22	44.85+1.61	0.33±2.69	0.662
First-week and second-week POST-PV	43.13+6.35	44.97+4.73	-1.84±5.08	0.215
First-week and second-week NoR	46.85+23.31	58.31+18.75	-11.46±12.14	0.005*

(*p < 0.05; PRE-PV: Pre-fatigue proprioception value; POST-PV: Post-fatigue proprioception value, NoR: Number of repetitions)

DISCUSSION

The findings revealed that the proprioception measured at 45° of knee flexion before and after fatigue had no significant impact in the group playing basketball for more than a year. The effect of KT on proprioception was not found to be statistically significant. However, the number of repetitions recorded in the fatigue protocol in both weeks differed significantly. In other words, the participants were able to perform a higher number of movements in the second week, implying that KT may be effective in facilitating the muscle and, thus, help releasing a higher number of movements. The literature offers diverse findings regarding the impacts of taping on muscle strength and endurance (28,29). While some studies argued that it contributes to increased muscle strength and endurance, others proposed vice versa (30,31). A relatively small sample size and random selection of the participants in these studies may have caused insufficient evidence for the effect of taping (4,31). A power analysis was conducted prior to the evaluation. The results of this analysis revealed that the number of individuals required to participate was three. Since we evaluated 13 participants in this study, it was thought to have enough participants. This showed that a sufficient number of individuals participated in this study. Han and Lee (32) designed a study with 30 healthy adults to investigate the impacts of KT on knee joint proprioception after quadriceps muscle fatigue. They evaluated knee joint proprioception on the dominant side at 30°, 45°, and 60° with and without taping before and after fatigue. Their findings showed that quadriceps fatigue adversely affected proprioception and that KT improved reduced proprioception due to fatigue (32). The results of the study of Han and Lee, which are similar to ours, are different. This may be because in our study, we evaluated proprioception only at 45° knee flexion and, in addition, Han and Lee did not evaluate fatigue.

Álvarez et al. (33) studied the impacts of KT on the fatigue of the lumbar extensor musculature among 99 healthy young people. As a result, they found that KT affected the processes leading to muscular fatigue (33). Similarly, in our study, it was found that KT had effect on muscular fatigue. Ahn et al. (34) carried out a study with 45 participants to investigate the effects of KT on the quadriceps muscles immediately after muscular fatigue. The participants were divided into three groups: the KT group, the placebo group, and the no-taping group. The groups were then recruited for the quadriceps strength test, the single-leg hop test, the active joint position sense test, and the single-leg static balance test. The authors concluded that the results of the strength test and the single-leg hop test were significantly better in the KT group, but taping did not have a significant effect on the results of the active joint position sense test and the single-leg static balance test. The common point of this study with the research of Ahn et al. (34) is the evaluation of proprioception and similarly the effect of KT on proprioception was not statistically significant. Another study proposed that KT may help restore reduced muscle strength following muscular fatigue; therefore, it may be beneficial for tired muscles (34). Choi and Lee (35) aimed to determine the impacts of the application direction of KT on the strength of the tired quadriceps muscles. Accordingly, they applied tapes to the quadriceps femoris muscle of 15 individuals. While seven tapes were applied from the origo to the insertion, eight were attached from the insertion to the origo. The results showed no significant difference by the application direction of KT, but it was thought that it could promote the strength of tired quadriceps muscles regardless of the application direction (34). Based on these studies, KB was found to have positive effects on fatigue in several research (33-35). In general, the findings mentioned above suggest that KT may reduce muscle fatigue by promoting endurance and be used as a supportive method to elevate endurance in a clinical context.

The present findings yielded no significant difference between the pre- and post-fatigue proprioception values in the first-week measurements, leading to the conclusion that this level of fatigue did not affect the proprioception values of the trained group (36). Moreover, the same was observed in the second-week measurements. Therefore, this finding then implies that proprioception might be less affected following fatigue in KT-applied participants; therefore, KT may be utilized to protect the joint and reduce the risk of injury, particularly among athletes. Besides, the comparison of the first- and second-week pre-fatigue proprioception measurements yielded no significant difference, as expected, since both measurements were performed under the same conditions. Contrary to expectations, there was no significant difference between the post-fatigue proprioception values in the first- and second-week measurements. Hops et al. (37) previously evaluated the joint position sense of 20 healthy female individuals pre- and post-KT under a fatigue protocol at knee flexion angles of 20° and 70°. Overlapping with the present findings, they found that taping in the participants with poor proprioception provided a significant improvement in joint position sense values before and after taping (37). In discordance with our study, proprioception was evaluated in various knee flexion angles in this study. It should be noted that adolescents engaging in sports activities for a long time bear a good level of proprioception, which may be the reason why the impact of KT was not statistically significant in the participant group (37). Bayramoğlu et al. (38) also found that fatigue from light and moderate exercise did not affect proprioception (38). In our study, the focus was the acute effects of KT, but different results were presented in which the focus was chronic effects of KT (8,39,40). Torres et al. (8) applied KT to the quadriceps femoris muscle (from the origin to the insertion) of 30 healthy young participants with the facilitation technique and measured proprioception at 30 and 60 degrees on an isokinetic dynamometer immediately and 24 hours after the application. Although they concluded with no significant findings, the results suggested that it may affect proprioception positively by improving passive movement sense (8). In their study, Callaghan et al. (39) evaluated the impacts of patellar taping on proprioception in patients with patellofemoral pain syndrome (PFPS). In conclusion, the authors found that patellar taping did not improve proprioception in all PFPS patients, but proprioception could be supported by patellar taping in PFPS patients with weaker proprioception (39). Yeong Sook et al. (40) applied KT to a study group of 30 people for four weeks, three times a week (totally 12 times) and found that KT increased range of motion and had analgesic effect on the knee joints in the elderly. In this study, apart from the other studies, proprioception and fatigue were evaluated in the same time. In addition, the population selection (adolescent basketball players) makes this study original. Depending on this scientific basis, it is thought that, this study both supports the other researches available in the literature and guide the researchers to develop new projects on this topic.

Limitation of This Study

This study was conducted on adolescent basketball players in order to find out the acute effect of KT on fatigue and proprioception following fatigue. So, it was our limitation not to have evaluated the effect of KT in a longer period. Another limitation is that proprioception was evaluated just while the knee joint

was going through flexion and just one flexion angle was chosen as target angle. In addition, not having a placebo group can be considered as another limitation. Because this study included healthy adolescent basketball players, it was not known how the results would have been in symptomatic individuals in different age ranges. Designing new research by using same protocol on individuals with different knee pathologies and between different age ranges can be recommended.

CONCLUSION

Within-group comparisons of pre- and post-fatigue proprioception values revealed no significant difference between both groups. While there was also no significant difference in pre-fatigue proprioception values between groups, it was also the case for post-fatigue proprioception values. However, the number of repetitions in the fatigue loading protocol significantly differed between the groups. Although Kinesio taping (KT) is not found to have effect on fatigue- related proprioceptive response, it was found to increase muscular endurance which was presented by the number of movement repetitions. This means that , KT may have valuable clinical effect on increasing the level of threshold of sports related injuries.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 26.06.2019, Decision No: 2019.06.18).

Informed Consent: Written consent was obtained from the patient participating in this study.

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 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 role of intravenous tranexamic acid for blood loss in total hip arthroplasty secondary to femoral neck fracture

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ABSTRACT

Aim: The aim of the study was to compare the efficacy of intravenous (IV) administration of tranexamic acid (TXA) in terms of bleeding volume, allogeneic blood transfusion (ABT) requirement, and complications in total hip arthroplasty (THA) secondary to osteoporotic femoral neck fracture (FNF).

Material and Method: A total of 165 patients who underwent THA on the background of FNF in our clinic were included in the study. Patients' demographic data, preoperative and postoperative blood parameters, the amount of blood loss calculated according to the Nadler formula, amount of ABT, and complications at the 90-day follow-up were recorded. The patients were divided into two groups those who received 15 mg/kg preoperatively and 10mg/kg IV TXA at the end of the operation (TXA group-89 patients) and those who did not receive TXA (Control group-76 patients) and the two groups were compared.

Results: The total amount of bleeding calculated according to the Nadler formula was significantly less in the TXA group (1659,68±320,86ml) compared with the Control group (1774,43±365,24ml) (p=0.033). The need for ABT was 42.86% in the TXA group and 57.14% in the control group, and this difference was statistically significant (p=0.008).

Conclusion: In patients who underwent THA on the basis of osteoporotic FNF, preoperative and postoperative administration of 2 doses of IV TXA significantly reduced total blood loss and the need for ABT. We suggest that IV TXA administration can be safely performed, especially in this patient group, to reduce the amount of bleeding and therefore the need for ABT by not increasing any thromboembolic complications.

Keywords: Total hip arthroplasty, tranexamic acid, blood loss, allogeneic blood transfusion, nadler

INTRODUCTION

The incidence of hip fractures after simple falls is on the rise as the proportion of the elderly population increases and bone mineral density decreases with age (1). However, it is estimated that more than 6 million hip fractures will have occurred by 2050 (2). Femur neck fractures (FNF) constitute the majority of hip fractures in the elderly and are often treated with the surgical option of hemiarthroplasty (HA) or total hip arthroplasty (THA). Although THA provides better functional scores and pain reduction compared with hemiarthroplasty, it also has disadvantages such as the risk of dislocation, prolonged surgery time, and increased perioperative bleeding (3). It has been reported that the mean perioperative total blood loss in THA can be 700-2000 ml and allogeneic blood transfusion (ABT) rates can range from 16% to 68% (4,5). ABT may result in a variety of complications, including the transmission of blood-borne diseases, immunologic reactions, increased periprostatic infection, increased costs, acute lung injury, allergic reactions, and death.(4) Due to these reasons, despite numerous studies conducted to reduce perioperative bleeding and the need for ABT, the use of antifibrinolytic agents has become increasingly popular recently. Tranexamic acid (TXA), a synthetic analog of the amino acid lysine, prevents fibrinolysis by blocking the lysine binding sites of plasminogen and thus stabilizes the clot by reducing the proteolytic activity on fibrinogen and fibrin monomers (6). TXA has been reported as an effective and relatively safe agent in reducing blood loss among antifibrinolytic agents (7).

Although there have been studies and meta-analyses on the use of TXA in THA applications, the dose, form, and time of administration of TXA are still controversial (8–12). Although there are publications reporting that the use of intravenous (IV), oral or topical TXA is superior to each other in studies, there is no consensus on issues

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such as multiple-dose, single-dose, or combined use of TXA, except for the use of TXA (11,12).

Although there are many studies on the use of TXA in THA performed on elective grounds, the number of studies on the bleeding amount, need for ABT, and complications of TXA in patients who underwent THA for osteoporotic FNF in the elderly population is limited (13,14). This patient profile often consisted of patients who were often excluded from TXA studies due to cardiac diseases, previous cerebrovascular events, or comorbidities. However, it is well-documented that ABT applications are even riskier in the elderly population (15). Hence, ABT should be avoided as much as possible in this age group. Therefore, in this study, we aimed to compare the amount of bleeding, the need for ABT, and postoperative complications in the elderly population in whom THA was applied on the background of FNF by comparing patients who received IV TXA with patients who did not receive TXA.

MATERIAL AND METHOD

The study was carriedout with the permission of Aydın Adnan Menderes University Clinical Researches Ethics Committee (E-21559114-804.01-20/01/2023-301616). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The archive records of our clinic between January 2013 and December 2020 were retrospectively reviewed, and patients over the age of 65 who underwent THA on the basis of FNF, patients who had at least 3 months of postoperative follow-up for symptomatic deep vein thrombosis (DVT) and had adequate records, and patients who underwent primary THA using the posterolateral approach were determined. Patients who underwent revision hip arthroplasty, patients with ischemic heart disease, cerebrovascular accident, known bleeding disorder, a history of thromboembolism such as DVT, chronic liver or renal failure, known sensitivity to TXA, incomplete archival records, and patients who could not be reached were excluded from the study. A total of 13 patients, 6 of whom were given TXA and 7 who were not given TXA, were excluded from the study because they died in the first 90 days of follow-up. A total of 165 patients who met these inclusion criteria were included in the study. Of these patients, 89 were in the group that received IV TXA and 76 were in the control group that did not receive TXA.

It was ensured that the preoperative hemoglobin (Hb) level was higher than 10 gr/dl in all patients for whom surgery was indicated. All patients underwent uncemented THA in the lateral decubitus position by surgeons experienced in arthroplasty through a standard posterolateral approach.

According to the TXA protocol we applied in THA, in the TXA group, the intravenous infusion was administered in 15mg/kg (Transamine®, 250 mg/2.5 mL IV Injectable Solution Teva Pharmaceuticals, Turkey) 100mL saline (0.9%) 30 min before the TXA skin incision, and again in the operating room, in 10mg/kg 100mL saline (0.9%) immediately after the fascia was closed. TXA was not administered in the other group.

40 mg/day enoxaparin sodium, which was started 12 h before the surgery prophylactically, was administered subcutaneously once a day to the patients and was used for 30 days after discharge. The patients were mobilized on the first postoperative day and followed up with the standard postoperative follow-up protocol. Demographic data, the amount of ABT, whether a drain was used or not, and operative risk according to the American Society of Anesthesiologists (ASA) classification were recorded. Preoperative and postoperative blood parameters on the 1st, 2nd, and 3rd days were recorded. The trigger point for ABT was determined as Hb < 8 g/dl (16).

The formula described by Nadler et al. (17) was used to calculate the amount of blood loss.

BBV-male(L)=(0,3669 × H3)+(0,03219 × W)+0,6041

BBV-female(L)=(0,3561 × H3)+(0,03308 × W)+0,1833

Hb loss was found by applying the estimated BBV, preoperative Hb, postoperative Hb and transfused Hb amount to the formula below.

Hb loss=BBVx(preoperative Hb–postoperative Hb)x10 dL/L+amount of transfused Hb

Patients were followed up for the presence of hematoma, infection, and DVT during hospitalization and the first three months after discharge.

Preoperative blood values, demographic data, estimated blood volume (EBV), ABT rates, estimated blood loss, length of hospital stay, and complications such as superficial or deep wound site problems, DVT, and pulmonary embolism (PE) in the first 90 days postoperatively were compared between the groups.

SPSS 22.0 for the Windows program was used for statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. Comparisons of two independent groups were made with Student's t-test when numerical variables met the normal distribution condition and with the Mann-Whitney U test when they did not. Rates in independent groups were compared using the Chi-Square Test. The statistical significance level was accepted as $p<0.05$.

RESULTS

When the demographic data and general characteristics between the two groups were compared, no difference was observed between the groups. All these data are summarized in **Table 1**. Comparison of preoperative mean blood values is shown in **Table 2**. It was found that there was no significant difference between the groups in terms of these values.

Table 1. Demographic and general data of the patients.

	IV TXA group (n:89)	Control group (n:76)	P value
Age (years) ±SD	72.10±5.15	71.55±4.56	0.474
Gender (Female/Male)	54/34	48/38	0.651
Height (cm) ±SD	165.66± 6.91	165.46±6.32	0.964
Weight (kg) ±SD	73.11± 10.52	74.11± 9.21	0.518
Body mass index (kg/m²) ±SD	26.69± 3.72	27.03± 3.15	0.533
Surgery time (minutes) ±SD	146.68± 24.92	145.06± 29.92	0.705
Lenght of stay hospital (days) ±SD	5.34± 1.91	6.57± 2.74	0.001
ASA score			0.388
ASA 1	5 (5.62%)	3 (3.95%)	
ASA 2	48 (53.93%)	51 (67.11%)	
ASA 3	32 (35.96%)	20 (26.31%)	
ASA 4	4 (4.49%)	2 (2.63%)	

Abbreviations: IV, intravenous; TXA, tranexamic acid

Table 2. Comparison of preoperative blood parameters of patients.

	IV TXA group	Control Group	P value
APTT	27.43±4.04	27.23±2.89	0.153
Protrombin time	13.63±1.71	13.88±2.31	0.431
INR	1.06±0.13	1.08±0.15	0.470
Thrombocyte	260.66±85.05	276.65±85.05	0.230
Hemoglobin	12.97±1.04	13.15±1.44	0.345

Abbreviations: IV, intravenous; TXA, tranexamic acid; APTT, activated partial thromboplastin time; INR, internationel normalized ratio

The comparison of Hb and Hematocrit (Htc) values between the two groups on preoperative and postoperative days is shown in **Table 3**.

Table 3. The mean hemoglobin and hematocrit values of the patients preoperatively and postoperatively on 0, 1, 2 and 3 days.

	IV TXA group	Control Group	P value
Hemoglobin			
Preop	12.97±1.04	13.15±1.44	0.345
Postop day 0	10.55±1.33	10.92±1.72	0.126
Postop day 1	9.86±1.31	9.89±1.76	0.922
Postop day 2	9.21±1.27	9.16±1.55	0.848
Postop day 3	9.09±1.07	9.02±1.11	0.684
Hematocrit			
Preop	38.27±3.85	39.53±4.58	0.056
Postop day 0	35.13±9.21	33.10±5.15	0.577
Postop day 1	32.96±9.19	29.65±6.05	0.343
Postop day 2	27.93±3.93	27.65±4.48	0.665
Postop day 3	27.39±3.06	27.42±3.37	0.945

Abbreviations: IV, intravenous; TXA, tranexamic acid

Total blood loss, total blood volume, total Hb loss, total Hb loss, transfusion amount, and ABT values, which were calculated using the Nadler formula, were compared in **Table 4**, and total blood loss, ABT amount and the total amount of ES transfused were less in the group given TXA (p=0.033, p=0.008, p=0.007, respectively).

Table 4. Total blood volume, total blood loss, Hb loss calculated according to Nadler's formula and need for ABT and transfused ES amount

	IV TXA group	Control Group	P value
Total Blood Volume	4.42±0.49	4.39±0.53	0.703
Total Blood Loss	1659.68±320.86	1774.43±365.24	0.033
Hb loss	222.76±50.36	234.73±53.10	0.140
ABT amount	33/89 (42.86%)	44/76 (57.14%)	0.008
Transfused ES amount	0.62±0.90	1.05±1.07	0.007

Abbreviations: IV, intravenous; TXA, tranexamic acid; Hb, hemoglobin; ABT, allogeneic blood transfusion; ES, erythrocyte suspension

When evaluated in terms of complications, DVT was seen in 2 patients in the TXA group at the 90-day follow-up, whereas DVT was seen in 1 patient in the control group. There was no significant difference between the groups in terms of complications such as DVT or PE (p=1.000).

DISCUSSION

With increasing life expectancy, the incidence of hip fractures is increasing and is expected to reach up to 6 million per year in the USA alone in the near future (18,19). THA is a frequently preferred technique after hip fracture and is a major surgical option with a bleeding rate of approximately 2000 ml (4,5). Although there are many studies on reducing the amount of bleeding and the need for ABT with the use of TXA in patients who underwent THA on elective grounds, the number of studies with TXA applications in patients who underwent THA on FNF grounds is limited (13,14,20). For this reason, we think that our study will contribute to the literature. Our study showed that TXA significantly reduced the amount of bleeding and ABT in patients who underwent THA on the basis of FNF compared with the non-TXA group. In our study, it was found that TXA resulted in a decrease of approximately 115 ml in the amount of bleeding and 14.28% in the amount of ABT with 2 doses of 15mg/kg IV preoperatively and 10 mg/kg IV immediately after fascia closure.

In a study examining the efficacy of TXA in patients who underwent total hip surgery on the basis of intra-articular FNF, 58 patients who underwent TXA and 137 patients who did not undergo TXA were compared. It was found that there was approximately a 31% decrease in the transfusion rate and a 28% decrease in hemoglobin level in the TXA group (14). In this study,

we think that comparing the amount of bleeding only from hemoglobin levels without using a method such as the Nadler formula may not give accurate results. In their randomized clinical trial, Watts et al. (13) reported a decrease of approximately 9% in the need for blood transfusion in patients who underwent arthroplasty on the basis of FNF compared with the placebo group in patients who received TXA, but this value was not statistically significant. Meanwhile, in our study, we think that TXA can be used safely since the amount of transfusion was significantly reduced by approximately 14% and the amount of bleeding by approximately 115ml (15.4%) in the TXA group.

Additionally, Lee et al. (21), in their prospective randomized study, compared the placebo group with TXA administered in 2 doses of 15mg/kg at doses similar to our study. In the placebo group, the total blood loss was 1326ml and the need for ABT was 58.8%, while in the TXA group, blood loss was 674ml, and the need for ABT was 26.5%. However, in this study, blood loss was determined by calculating the amount coming from the drain and intraoperative bleeding. Based on the literature review, very different amounts of ABT and bleeding have been observed in applications of TXA. These differences may be caused by factors such as different methods used to calculate the amount of bleeding and different trigger points in Hb values for the need for ABT. Further, TXA has an approximately 2-hour half-life, and its plasma concentration reaches its maximum within one hour of administration. In the studies, TXA administered at different times and doses may also result in differences in ABT and bleeding amounts. There is no consensus on the dose and time interval of TXA, and there are different studies on this subject. In a study comparing 3 groups of 10mg/kg TXA, 15mg/kg TXA, and placebo group in THA, it was reported that 10mg/kg or 15mg/kg administration was also effective in reducing the amount of bleeding, but the need for ABT was significantly less in the 15mg/kg dose group than in the 10mg/kg group (22). In their study, Imai et al. (23) investigated the effect of TXA on intraoperative and postoperative bleeding amounts by dividing into 5 groups control group without TXA, single dose preoperative, single dose postoperative, double dose preoperative and 6 h postoperative, double dose postoperative and 6 hours postoperative. They emphasized that TXA administered preoperatively before anesthesia was effective in reducing the amount of bleeding, but double-dose administration of TXA, repeated at 6 h, was more effective in providing therapeutic plasma concentration. In this study, 2 doses, preoperatively and immediately after fascia closure, were not compared. In our study, we think that one of the reasons why iv TXA administration in the form of 2 doses before surgery and after fascia closure was significantly effective in reducing the amount of bleeding and the need for ABT was that we provided a sufficient amount of therapeutic plasma concentration by administering an appropriate dose and double dose.

Apart from the IV use of TXA, options such as oral, topical, or combined use are applied in the literature (9,20,24). In a meta-analysis of 964 patients comparing THA patients treated with topical and IV TXA, it was shown that there was no significant difference between the groups in total blood loss, the need for ABT, and the occurrence of DVT-like complications (24). Although it is thought that topical use may be safer in terms of side effects compared with IV use, there is no compelling evidence for this. When topical use options are considered, there are many options in the literature, such as application after fascia closure, through a drain, in the acetabular or femoral preparation. It is well-established that, intraoperative bleeding as well as postoperative bleeding causes significant blood loss. Therefore, it is evident that topical options such as fascia closure or drain applications may not have any impact on intraoperative bleeding. However, as in our study, we think that IV TXA administered preoperatively will be effective in reducing intraoperative bleeding. Furthermore, in a study conducted in healthy individuals, it was found that the plasma concentration of TXA reached the maximum level at the 1st hour after IV administration in individuals administered IV single dose TXA and that 30% of TXA was excreted in 1 hour, 55% was excreted in the 3rd hour and 90% in 24 hour (25). Hence, we think that in our study, effective plasma concentration that will reduce bleeding especially in the intraoperative process is achieved with IV TXA administration before anesthesia induction, while the effective plasma concentration of TXA, which started to decrease towards the end of the surgery, was achieved with the re-administration of TXA as a second dose, and the effective plasma concentration was reached for bleeding observed in the early postoperative period. For this reason, we are of the opinion that IV TXA, which we administer before and after surgery, is an effective and successful application in reducing blood loss.

Due to the retrospective design of our study, only patients who were diagnosed after clinical suspicion were evaluated in terms of thromboembolic events such as DVT and PE. Subclinical or clinically asymptomatic thromboembolic complications may not be diagnosed because vaso-occlusive events are not routinely screened by ultrasonography or any additional tests. One of the limitations of our study is the problems arising from this retrospective design. Moreover, the fact that the amount of intraoperative bleeding was not measured can be considered one of the shortcomings of the study.

CONCLUSION

We think that this study, which we have done in patients over 65 years of age who underwent THA after FNF in osteoporotic conditions, will contribute to the literature as it has compared the effectiveness of TXA in a more specific group. Our study suggests that TXA is effective and safe on blood loss and the need for ABT in FNF secondary THA applications in the osteoporotic background. Nevertheless, we believe that studies involving a large number of patients, in a prospective design, which evaluate all forms of TXA, including combined forms, may provide clearer results on its efficacy and safety.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Aydın Adnan Menderes University Clinical Researches Ethics Committee (E-21559114-804.01-20/01/2023-301616).

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 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 retrospective analysis on mucormycosis in patients with hematological diseases: a single center experience from Turkey

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ABSTRACT

Aim: Mucormycosis is an acute, invasive, devastating and highly fatal fungal infection, affecting particularly immunocompromised patients; fortunately, it is rare. This study aimed to describe the attitude of mucormycosis in patients with a hematological disease, and to evaluate the risk factors associated with mortality.

Material and Method: We retrospectively assessed the demographic and clinical data of patients who were diagnosed with mucormycosis in Erciyes University Hematology and Bone Marrow Transplantation Center, between 2010 and 2020. The study was included 34 patients with a history of either hematological malignancy or hematopoietic stem cell transplantation.

Results: Twenty-seven patients had proven infection, and the others had possible infection. The most frequent underlying disease was acute leukemia. Seven-teen patients had a history of allogeneic transplantation, and frequency of mucormycosis was 3.5% among allogeneic transplant recipients. The most frequent site of infection was the rhino-orbital region (85.3%). Forty-seven percent of patients presented with acute orbital symptoms. Fifteen patients were on a mucor-active antifungal (posaconazole and liposomal Amphotericin B) prophylaxis or treatment at the time of diagnosis. All patients received liposomal Amphotericin B and seven patients received posaconazole additionally as initial therapy. Surgical debridement was performed in 91.1% of patients. The two-year mucor-related mortality rate was 44.1%. The survival curves were significantly lower in patients with concomitant fungal pneumonia, allogeneic transplantation and also in patients who were receiving mucor-active antifungal drugs at the time of diagnosis.

Conclusion: Mucormycosis remains a significant problem for hematology clinicians despite the expanding use of antifungal prophylaxis. Moreover, breakthrough infections indicate rising danger regarding resistant agents. We also highlight that, most of the patients receiving broad-spectrum antifungal prophylaxis are more fragile and more complicated patients, which put them at increased baseline risk for mucormycosis, and deserve more attention.

Keywords: Invasive fungal infection, mucormycosis, hematological malignancy, hematopoietic stem cell transplantation

INTRODUCTION

Invasive fungal infection (IFI) is a remarkable cause of morbidity and mortality in immunocompromised states. Particularly, mucormycosis is prominent among other species with a high fatality rate. Mucormycosis is a standard nomenclature used for invasive necrotizing infections caused by fungi belonging to the Mucorales order (old name Zygomycetes). The well-known members are Rhizopus, Rhizomucor, Mucor, Lichtheimia (Absidia), and Cunninghamella species (1). Since Mucorales are ubiquitous fungi and can release airborne spores, it is easy to be exposed anywhere. Although they are not resistant to intact human immunity, they can grow rapidly and cause devastating infections in immune-compromised patients.

The well-known risk factors of mucormycosis include diabetes mellitus, glucocorticoid treatment, penetrating trauma, or burns. Also, the patients with hematologic malignancy and hematopoietic stem cell transplantation (HSCT) are perfect hosts for mucormycosis.

In fact, the characteristics of infection vary depending on the factors such as geography, economy or features of the population studied. Hematologic malignancies are the most frequent underlying disease in Europe, whereas diabetes is more frequent reason in the Middle East, India, and Africa (2-5). In patients with hematological malignancy or HSCT, mucor frequency was reported between 2–8%, and the mortality rate could reach up to 65% (3,6-11).

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In this study, we aimed to evaluate the course of mucormycosis infection and associated risk factors in patients with hematological disease.

MATERIAL AND METHOD

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 21.04.2021, Decision No: 2021/293). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study design

We retrospectively collected the data of mucormycosis in patients with a history of either hematological malignancy or HSCT. The study was conducted in Erciyes University Hematology and Bone Marrow Transplantation Center in Turkey, between 2010 and 2020.

Thirty-four patients with diagnosis of mucormycosis were included. All but one had deep tissue biopsy. Thus, the data was recorded regarding histopathologic and direct microscopic examination and cultures. Based on the 2019 criteria provided by the European Organization for Research and Treatment of Cancer/ Mycosis Study Group (EORTC/MSG), patients were categorized into three diagnosis subgroups: proven, probable, and possible mucormycosis (12).

Proven mucormycosis was defined as the disease with mycologic evidence; positive histopathologic and direct microscopic examination and/or positive specimen culture obtained from a sterile tissue biopsy.

Probable mucormycosis required the presence of mycologic evidence in the sample obtained by bronchial lavage, sinus aspiration or sputum, along with typical clinical and/or radiological features.

Patients with typical clinical and/or radiological features and disease progression compatible with mucormycosis, but without any mycological evidence, were defined as possible mucormycosis.

The date of diagnosis corresponded to the day of the biopsy.

The last 30 days preceding the diagnosis of mucormycosis were considered for iron chelation, antifungal prophylaxis, corticosteroid, and immunosuppressive treatment. In addition, steroid exposure was recorded if >8 mg/day of methylprednisolone (or equivalent) for more than 21 days.

Early clinical response was assessed in terms of resolution of symptoms and fever at on the 15th day of diagnosis.

Statistical Analysis

Statistical analysis were performed using the commercial statistical package SPSS (IBM SPSS Statistics 24). Statstical significant was considered as $p<0.05$. According to the normality of distrubution of variables 'Independent Sample-t' test (t-table value) and 'Mann-Whitney U' test (Z-table value) were used to compare the two independent groups. Relationships between categorical variables were compared using 'Fisher's exact test' (chi-square test), 'continuity correction' or 'Pearson-χ2 tests', as appropriate. Survival curves were constructed using 'Kaplan-Meier analysis' and 'Cox-Regression analysis' was performed for identifying factors effecting survival.

RESULTS

The study included 34 patients diagnosed with mucormycosis, of which 21 (61.8%) were male. The mean age was 45.6±15.3 (range 19–70) years. Acute leukemia was the most common underlying disease (20 patients, 58.8%). Fourteen (41.2%) patients were in remission in terms of underlying disease at the time of mucor diagnosis.

During the study period, a total of 457 allogeneic HSCT was performed in our center. The frequency of mucormycosis was 3.5% among these patients. Seventeen patients were allogeneic transplantation recipients, and 11 of them were from full-match sibling donors. Patient characteristics are displayed in **Table 1**.

The most frequent site of infection was rhino-orbital region (n:29, 85.3%), and three patients presented with pulmonary mucormycosis (**Table 2**). In addition to these pulmonary mucor patients, 13 patients had preexisting or concomitant pulmonary fungal infection confirmed with imaging, but not specified.

Table 2. Site of infection and symptoms

	N (%)
Site of infection	
Sino-orbital	29 (85.3)
Cerebral	1 (2.9)
Pulmonary	3 (8.8)
Gastrointestinal	1 (2.9)
Symptoms	
Periorbital swelling and pain	16 (47.0)
Facial pain	13 (38.2)
Fever	25 (73.5)
Headache	6 (17.6)
Oral-palatine lesion	5 (14.7)
Nasal congestion	3 (8.8)

Table 1. Characteristics of patients, survived and expired because of mucormycosis

	Total n=34 n (%)	Expired n=15 n (%)	Survived n=19 n (%)	P*
Age mean, years ± SD (min-max)	45.6 ±15.3 (19-70)	42.4 ±16.1 (19-68)	48.1±14.6 (26-70)	p=0.295
Gender Male	21 (61.8)	7 (46.7)	14 (73.7)	χ2=1.573 p=0.210
Status of underlying disease				χ2=0.015 p=0.901
Active	20 (58.8)	9 (60.0)	11 (57.9)	
Remission	14 (41.2)	6 (40.0)	8 (42.1)	
Underlying disease				
AML	20 (58.8)	9 (60.0)	11 (57.9)	
ALL	4 (11.8)	2 (13.3)	2 (10.5)	
Lymphoma	3 (8.8)	1 (6.6)	210.5)	
MDS	1 (2.9)	0	1 (5.2)	
Aplastic anemia	1 (2.9)	1 (6.6)	0	
Other	5 (14.7)	2 (13.3)	3 (15.7)	
Transplantation history				χ2=3.135 p=0.077
No	16 (47.1)	4 (26.7)	12(63.2)	
Yes	18 (52.9)	11 (73.3)	7 (36.8)	
Auto- HSCT	1 (5.6)	1 (9.1)	0	
Allo- HSCT	17 (94.4)	10 (90.9)	7 (100)	
Full-match	11 (64.7)	6 (60.0)	5 (71.4)	
Haplo identical	6 (35.2)	4(40.0)	2 (28.6)	
GVHD				p=0.783
No	7 (38.9)	4 (36.4)	3 (42.9)	
Yes	11 (61.1)	7 (63.6)	4 (57.1)	
Comorbidity[1]				p=0.451
No	24(70.6)	12 (80.0)	12 (63.2)	
Yes	10 (29.4)	3 (20.0)	7 (36.8)	
Antifungal prophylaxis[2]				p=0.257
No	8 (23.5)	2 (13.3)	6 (31.6)	
Yes	26 (76.5)	13 (86.7)	13 (68.4)	
Posaconazole	11 (42.3)	6 (46.2)	5 (38.5)	χ2=1.958 p=0.581
Voriconazole	5 (19.2)	2 (15.4)	3 (23.1)	
Fluconazole	6 (23.1)	2 (15.4)	4 (30.7)	
L-AmB	4 (15.4)	3 (23.0)	1 (7.7)	
Steroid use[2]				χ2=0.377 p=0.539
No	19 (55.9)	7 (46.7)	12 (63.2)	
Yes	15 (44.1)	8 (53.3)	7 (36.8)	
Immunosuppressive[2]				p=0.718
No	24 (70.6)	10 (66.7)	14 (73.7)	
Yes	10 (29.4)	5 (33.3)	5 (26.3)	
Chelator[2]				p=0.889
No	26 (76.5)	11 (73.3)	15 (78.9)	
Yes	8(76.5)	4 (26.7)	4 (21.1)	
Deferoxamine	1 (2.9)	-	1 (25.0)	p=1.000
Deferosirox	7 (20.5)	4 (100.0)	3 (75.0)	
Mucormycosis relapse				p=0.902
No	26 (76.5)	11 (73.3)	15 (78.9)	
Yes	8 (23.5)	4 (26.7)	4 (21.1)	
Concomitant fungal pneumonia				χ2=5.670 p=0.017
No	18 (52.9)	4 (26.7)	14 (73.7)	
Yes	16 (47.1)	11 (73.3)	5 (26.3)	
Early response				p=0,000
No	8 (23.5)	8 (53.3)	0	
Yes	26 (76.5)	7 (46.7)	19 (100)	
Hospitalization[2]				p=0.128
Yes	24 (70.6)	13 (86.7)	11 (57.9)	
No	10 (29.4)	2 (13.3)	8 (42.1)	

[1]Diabetes mellitus, chronical lung disease, or rheumatismal disease, [2]at the time of symptom onset, *Relationships between categorical variables were compared using the 'Fisher's exact test' (chi-square test), 'continuity correction' or 'Pearson-χ2 tests', as appropriate

According to the EORTC criteria, 27 (79.4%) patients had proven infection, and the others had possible infection. There were no cases labeled as probable infection. Histopathology was diagnostic in 79.4% of subjects, culture was positive in 38.2% (n:13), and Rhizopus sp. was the most frequent species (n:7/13). Eight out of 13 patients with culture growth were on posaconazole prophylaxis (**Figure 1**). Twenty-six (76.5%) patients were on antifungal prophylaxis or treatment at the time of diagnosis, and 20 of them received mold-active antifungals.

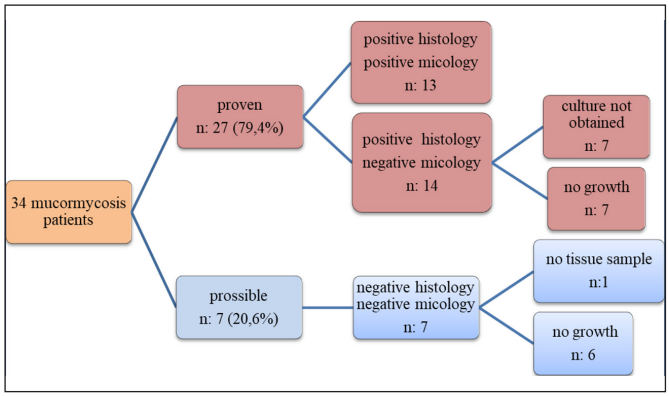

Figure 1. Distribution of patients according to EORTC criteria and diagnostic tools.
EORTC: European Organization for Research and Treatment of Cancer (2019)

Sixteen patients (47.0%) presented with acute orbital symptoms such as swelling, erythema, and pain in the periorbital region. The other common presenting symptoms were facial swelling and pain mainly localized at the maxillary area, palatine ulcer with necrosis, headache, and nasal congestion (**Table 2**). The median time from the onset of symptom to treatment was 2.5 days (min-max 1–7days).

Twenty-four patients (70,6%) developed infections during hospitalization, and 11 of them were transplant recipients. Twenty out of 34 patients (58,8%) were diagnosed in Autumn. The seasonal variation is demonstrated in (**Figure 2**).

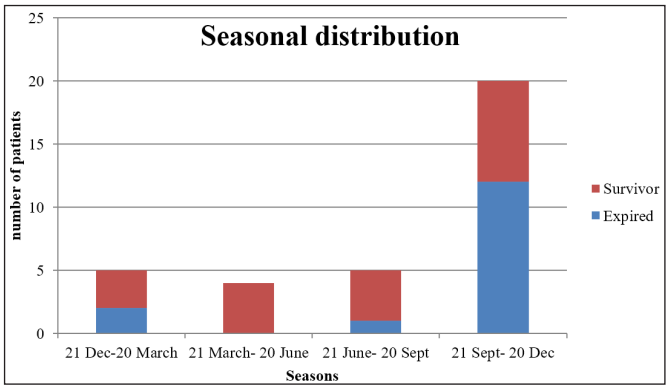

Figure 2. Distribution of patients according to seasonal variation

Twenty-three patients had a platelet level lower than 50×10^3 cell/mcL, 11 had absolute neutrophil count lower than 500 cell/mcL, and 14 had lymphocytes lower than 400 cell/mcL at diagnosis. However, there was no significant association between mortality and cytopenias (**Table 3**).

The median time to mucor diagnosis from transplantation was 0.35 years (min-max: 0.01–5.8), and from diagnosis of malignancy was 1.34 years (min-max: 0.25–8.55).

All patients received liposomal amphotericin B (L-AmB) at a dose of 5–10 mg/kg, and seven patients received additional posaconazole as initial therapy. However, posaconazole did not provide any significant advantage in terms of mortality or survival time. Thirty-one (91.1%) patients received surgical intervention in addition to medical treatment.Early clinical response was achieved in 26 (76.5%) patients on the 15th day. The remaining eight (23.5%) patients expired within 21 days due to mucormycosis infection; six were HSCT recipients. The median treatment duration was 39 days (min-max 4–117 days).

Sixteen patients received maintenance treatment with posaconazole (median 30 days, min-max 10–150 days). Mucor infection relapsed in eight patients (34.7% in responsive patients) after an average of 95.7 (±23.8) days from the first diagnosis (min-max 72–140 days), and six of them were on posaconazole maintenance (mean time to relapse, 95.7 (±23.8).

Table 3. Laboratory tests for mucormycosis patients at the time of diagnosis

	Expired (n=15)		Survived (n=19)		p/z*
	x̄±S.S.	Median [Min-Max]	x̄±S.S.	Median [Min-Max]	
D-Dimer (ng/ml)	2559.90±3235.67	1850.0 [269.0-11360.0]	2604.74±2631.70	1080.0 [390.0-8730.0]	Z=-0.092 p=0.927
LDH (U/L)	563.87±1013.89	256.0 [127.0-4157.0]	270.26±94.58	254.0 [130.0-433.0]	Z=-0.347 p=0.729
Fibrinogen (mg/L)	516.75±186.54	555.5 [227.0-768.0]	408.56±156.00	415.5 [175.0-827.0]	t=1.716 p=0.097
C-RP (mg/L)	102.71±111.25	50.0 [4.0-328.0]	66.47±81.26	37.0 [1.0-285.0]	Z=-1.012 p=0.311
Ferritin (µg/L)	2364.41±1508.21	1790.0 [694.0-5096.0]	2565.79±1854.29	2130.0 [473.0-9029.0]	Z=-0.122 p=0.903
Iron (µg/dl)	159.08±94.01	148.0 [40.0-340.0]	180.63±95.32	170.0 [19.0-396.0]	t=0.632 p=0.532
T Sat (%)	0.88±0.61	0.81 (0.08-2.49)	0.66 ±0.20	0.75 (0.38-0.90)	P=0.229
Neutropil (10^3/µg)	2.40±2.85	0.8 [0.0-7.7]	2.48±2.18	2.1 [0.0-6.4]	Z=-0.434 p=0.664
Lymphocyte (10^3/µg)	0.99±1.68	0.5 [0.1-6.8]	1.15±2.09	0.7 [0.1-9.4]	Z=-0.382 p=0.702
Platelets (10^3/µg)	64.73±84.66	15.0 [5.0-262.0]	64.06±75.14	31.0 [9.0-230.0]	Z=-0.706 p=0.480

*According to the normality of distribution of variables 'Independent Sample-t' test (t-table value) and 'Mann-Whitney U' test (Z-table value) were used to compare the two independent groups. LDH: Lactate dehydrogenase, C-RP: C reactive protein, T Sat: transferrin saturation

Two-year mucor related mortality rate was 44.1%. The Median follow-up was 4.2 months (min-max 0–24.0), and mean survival time was 13.85 months (95% CI, 10.0–17.7%). The mucor-related mortality was not different in the analysis of subgroups based on gender, underlying disease, antifungal prophylaxis or graft versus host disease (GVHD) (p>0.05). The mortality was higher in patients with transplantation history (61.1% vs 25.0%) but it was not statistically significant. Likewise, there was no significant difference between expired and survived patients in terms of inflammatory markers, iron parameters or blood counts (p>0.05) (**Table 3**). The Mortality was significantly higher in patients with concomitant fungal pneumonia ($\chi 2=5.670$; p=0.017) and with no early clinical response (p=0.000) (**Table 1**). The survival curves were significantly lower in patients with concomitant fungal pneumonia and allogeneic transplantation and also in patients who were receiving mucor-active antifungal drugs (posaconazole and L-AmB) for prophylaxis or treatment of the previous infection (**Figure 3**).

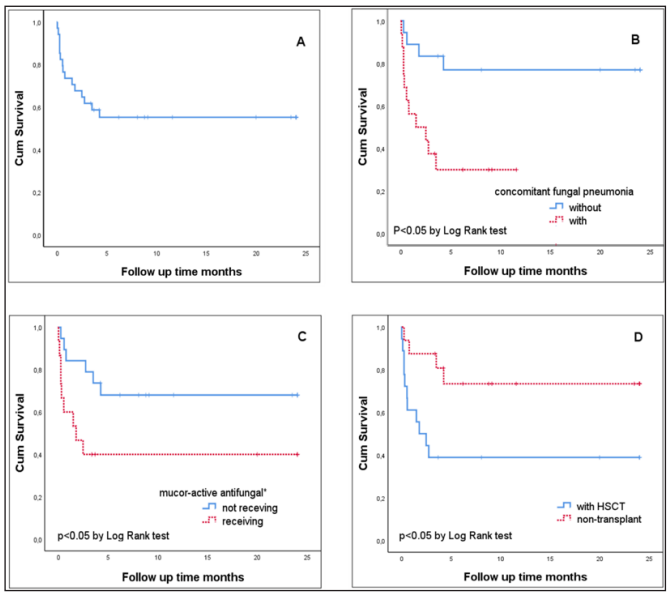

Figure 3. 2-year survival curves for the patients with mucormycosis, overall survival (A), for patients with or without concomitant fungal pneumonia (B), for patients receiving antifungal prophylaxis/ treatment or not at the time of mucor diagnosis (C), for patients with or without HSCT history (D) (Kaplan–Meier analysis)

HSCT: hematopoietic stem cell transplantation, *Posaconazole or liposomal Amphotericin B

DISCUSSION

Although effective prophylaxis and treatment options are developing for fungal agents, we still have limited solutions for mucormycosis. Moreover, the effect of broad-spectrum antifungal prophylaxis on the risk of mucor infection is a matter of debate. Some studies highlight the increasing use of mold-active antifungals (in particular voriconazole) as responsible for the higher rate of mucormycosis (1,9,13-17). On the contrary, Abidi et al. (18) reported similar results between the groups with or without voriconazole exposure. They emphasized that the enlargement of the risk population is responsible for the rising number of cases.

In current practice all patients with acute leukemia and HSCT receive antifungal prophylaxis during chemotherapy and neutropenic period, or posttransplant period, in some degree. In our cohort, more than three quarters of patients were receiving a mold-active antifungal at the time of mucor diagnosis. Eleven patients developed mucormycosis under posaconazole prophylaxis, and four patients were under L-AmB (3 mg/kg) treatment for fungal pneumonia. These patients displayed worse survival curves (**Figure 3**).

Invasive breakthrough fungal infections and also mucormycosis have been associated with a higher mortality rate reaching 70% in hematologic cancer patients (1, 19). Recently, a retrospective study from the USA reported 103 breakthrough mucor infections in patients with hematologic malignancy, and 16 of them were either under mucor-active antifungal treatment or prophylaxis such as posaconazole, isavuconazole and AmB. The mortality was significantly higher in these patients than those on other mold-active antifungals (20).

These findings could indicate resistant infections. On the other hand, most of these patients receiving broad-spectrum antifungal prophylaxis are more fragile and are complicated with a hematologic malignancy or bone marrow transplantation, which put them at increased baseline risk for mucormycosis.

The distribution of clinical manifestations has been variably reported in the literature due to the divergent factors such as risk population, geography, and social aspects. Pulmonary disease is the most common presentation in mucor patients with hematological malignancy based on reports from France, Israel, and Germany (3,21,22). Other studies from India, South America, the Middle East, and Africa display rhino-orbito-cerebral disease predominance (5,2-25). In the present cohort, the rhino-orbital region was the most frequent site of infection by a wide margin; however, 13 out of 29 rhino-orbital diseases had concomitant pulmonary fungal infection unspecified. In clinical practice, our patients with a prediagnosis of fungal pneumonia receive mold-active antifungal treatment empirically, primarily targeting aspergillus infection. To differentiate pulmonary IFI, isolation of agents through a proper biopsy is not possible in the majority of the patients. Moreover, overlap infections may easily be overlooked. So, the low proportion of pulmonary presentation can be deceptive for our population.

The rhino-orbito-cerebral infection usually starts in the nasal sinus and spreads to the palate, orbits, skull base, and brain. Accordingly, headache, facial pain, and nasal discharge are the most frequently reported symptoms for presentation (26,27). In our study, the most frequent symptom was unilateral orbital swelling, and the following was facial pain. In fact, fever was also present in most of the patients. However, it can be complicated with some factors such as neutropenia, other infections, and drug reactions which are quite common for our inpatients. Orbital or facial complaints should be considered alarming symptoms and deserve more attention.

There are some challenges in diagnosis. The reference method is a direct macroscopic and microscopic examination and culturing of biopsy fragments. Histopathologic identification of fungal elements compatible with Mucorales is crucial because it can reveal the fungus as a pathogen. Also, histopathology can define angioinvasive necrotic inflammation. However, culture is negative in a large proportion of the patients. This fungus is very fragile in nature, therefore sampling and transport issues are critical. In addition, culture possesses the possibility of contamination during sampling or laboratory process (28, 29). Samples using bronchial lavage and sinus aspiration are not valuable since diagnosis requires sterile tissue biopsy from the affected organ. However, proper tissue biopsy can be difficult due to localizations or thrombocytopenia. At this point, the management of thrombocytopenia requires extra attention. Furthermore, in the cases that have been already under mold-active antifungals, growth could be suppressed, or fungus may present atypical morphological features(30).

There is no reliable, standardized laboratory technique for mucormycosis for now. Serological tests and molecular methods are under investigation but have limited utility in identifying mucormycosis (4,31,32). Thus, the absence of culture positivity or histological evidence should not exclude the diagnosis if the clinical picture is significantly suggestive. The present study included seven patients diagnosed with possible mucormycosis according to EORTC criteria. In five of these patients, the biopsy was performed under L-AmB. There was no mycological or histological evidence in these patients, despite a highly suggestive clinical course for mucormycosis. These patients had rhino-orbital infections, and endoscopic examination was feasible; thus, the specific necrotic lesion could be observed directly. However, for pulmonary or disseminated disease to prove mucormycosis can be a real challenge, and maybe some of the patients with these features are overlooked.

In this high-risk population, not only an early-aggressive diagnostic approach, but also prompt initiation of mucor-effective antifungal treatment and maintaining enough long is life-saving. In a retrospective study on treatment, Camilos et al. (33) reported that delaying treatment resulted in a 2-fold increase in mortality rate. The breakpoint (between early and delayed treatment) was the 6th day of onset of symptoms. Regarding the median time from initial symptom to initiation of treatment, Axell-House et al. (20) reported six days, and Lanternier et al. (3) said two weeks in all and one week specifically in HSCT recipients. This period was shorter in our study (median 2.5 days), nevertheless this advantage did not improve the outcomes. We should point out that, we did not report fever as an initial symptom because most patients were complicated with another infection

About 80% of our patients were inpatient at the onset of symptoms; thus, empirical treatment could be started soon upon biopsy. Although the result is not statistically significant, mortality was higher in hospital-acquired infections than community gained (54% and 20%, respectively). Most of these inpatients had active underlying disease and were on chemotherapy.

There are some restricted studies on treatment and most of the data are coming from retrospective analyzes. L-AmB is still the most effective agent and combination with surgical debridement is highly suggested because of survival advantage (3,23,31,34,35).

In present study, mucor-related mortality was lower than previous reports for patients with hematologic malignancy (44.1%) (2,3,10,11,15). In many reports, localization of infection is an important determiner in mortality and mortality is higher in pulmonary disease (3,5,23). The difference between localizations was not significant in our cohort, probably due to less number of patients with involvement other than rhinoorbital region. However, mortality was significantly higher in patients with concomitant fungal pneumonia. These pulmonary infections were not able to specified, and maybe some of them were mucor infections.

The lesser number of patients is the main limitation of our study. Moreover, most of the patients suffered from a magnitude of complex risk factors such as cytopenia, antibiotics, antifungals, chemotherapy, and immunosuppressors. So it was not easy to assess the contribution of these factors with the outcomes.

In conclusion, we attempted to determine the attitude of mucormycosis in patients with hematologic malignancies and bone marrow transplantation. This study is noteworthy regarding the study period and the

number of patients for a single-center experience. Since mucormycosis is a rare infection, the accumulation of experiences will constitute the data pool. We want to emphasize the limited utility of the prophylactic approach. Early suspicion and prompt initiation of the treatment remains the key in this precarious population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 21.04.2021, Decision No: 2021/293).

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 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 risk scoring systems for the prediction of clinical outcomes in nonvariceal upper gastrointestinal bleeding: a prospective randomized study

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ABSTRACT

Aim: Non-variceal upper gastrointestinal bleeding (UGIB) is a typical gastrointestinal emergency. Detection of high-risk patients is crucial to organize medical care accordingly. This study aims to compare risk assessment scores for their ability to predict prognosis in nonvariceal-UGIB.

Material and Method: Adult patients with nonvariceal-UGIB applied to the emergency department were recruited prospectively. Clinical and Complete Rockall score (RS), Glascow-Blatchford score (GBS), AIMS65, and T-Score were compared for endpoints: (1) need for endoscopic treatment, (2) hospitalization, (3) rebleeding, and (4) 30-day mortality.

Results: A total of 469 patients were included. While 133 (28.0%) patients were discharged within 24 hours, 336 (72.0%) were hospitalized. The median length of hospital stay was 6.6 (0.0-8.0) days. Endoscopic treatment and transfusion were required in 109 (23.0%) and 255 (54.0%) patients, respectively. Rebleeding was observed in 36 (8.0%) patients. The 30-day mortality rate was 11.0 %. Complete Rockall score was superior among all risk scores regarding the prediction of the need for endoscopic treatment (AUC: 0.707, $p<0.001$) and hospitalization (AUC: 0.678, $p<0.001$). AUC values of AIMS65, Clinical RS, Complete RS, GBS, and T-score were 0.688, 0.601, 0.634, 0.631, and 0.651, respectively ($p>0.05$). AIMS65 score (AUC: 0.810, $p<0.05$) was superior to the clinical RS and GBS at predicting 30-day mortality. However, there was no difference between the AIMS65 score and the other scores of areas under the curve ($p> 0.05$).

Conclusion: Complete RS and AIMS65 scores are valuable tools to determine UGIB-related endpoints (need for intervention, hospitalization, rebleeding, and mortality). Identifying high-risk patients using the risk scoring systems and performing endoscopy in this group may improve clinical outcomes, while their sensitivity is inadequate in the low-risk patients.

Keywords: Gastrointestinal hemorrhage, endoscopy, risk assessment, prognosis

INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is one of the most common gastrointestinal emergencies confronted by clinicians in emergency departments (ED). Early endoscopy for the management of UGIB has gained general acceptance. It is useful in patients with persistent active bleeding and preventing recurrent bleeding, which can significantly reduce morbidity and mortality (1-5). The optimal endoscopy timing for patients with UGIB has been defined by several evidence-based guidelines and expert reviews within the first 24 h after admission following hemodynamic resuscitation (6-8).

However, the applicability of this recommendation is not always achievable. One-fifth of all patients with peptic ulcer bleeding had a clean ulcer base at the endoscopic examination. The risk of rebleeding is low (3%) in these patients, and endoscopic management could easily be performed without hospitalization (9-13). Therefore, the suggestion of early endoscopy for patients presenting with UGIB to the ED is doubtful. Numerous scoring systems have been designed to classify high-risk patients and differentiate them from lower-risk patients (14-22). Gastrointestinal system bleeding risk score systems have been proposed to predict early clinical outcomes, including the need for endoscopic treatment and hospitalization, rebleeding, and mortality (23). Despite the benefits mentioned above, employing these scores in clinical management still requires further studies.

In this prospective single-center study, we aimed to

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compare five risk assessment scores (clinical and complete Rockall score (RS), Glasgow Blatchford score (GBS), AIMS65, and T-Score for their ability to predict significant endpoints in adult patients with non-variceal UGIB.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital Scientific Researches Ethics Committee (Date: 02.09.2020, Decision No: E1/1051/2020). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Data were collected from consecutive adult patients (≥18 years) with symptoms and signs of UGIB admitted at the hospital between February-2019 and February-2020. UGIB is the presence of hematemesis, melena, or bloody nasogastric aspirate. All consequent patients who underwent upper gastrointestinal endoscopy with UGIB diagnosis were enrolled prospectively following an approved informed consent. Patients presenting with variceal bleeding and patients without informed consent forms were excluded from the study.

Management

All patients presenting with upper gastrointestinal bleeding were initially evaluated in the emergency department and were consulted by the gastroenterologist for bleeding. The clinical RS, GBS, AIMS65, and the T-score were calculated as pre-endoscopic, and Complete RS was calculated as post-endoscopic score by a gastroenterologist. Pantoprazole infusion (8mg/h following 80mg bolus) was promptly administered to all patients with UGIB. Transfusion with erythrocyte suspension (ES) was applied to patients with a hemoglobin level of less than 8g/dL. Blood transfusion was given to patients with a low hemoglobin level of less than eight g/dl. For patients with a hemoglobin (Hg) level between 8 and 9g/dl, transfusion was performed based on the patient's age, comorbidities, and hemodynamic status.

Endoscopy was performed within the first 12 or 24 hours based on the patient's hemodynamic status, decrease in hemoglobin level despite blood transfusion, and presence of active bleeding findings. Furthermore, an endoscopy was performed within the first 24 hours in patients who did not have evidence of severe bleeding, preferably to make an early discharge decision. Endoscopy time was calculated based on the admission time to the ED. Endoscopic treatment was performed in the presence of high-risk stigmata of recent hemorrhage (SRH): actively bleeding (spurting /oozing) or non-bleeding visible vessels. In case of endoscopic treatment failure, patients were consulted for interventional radiology or surgery. The clinician made the decision to be discharged or hospitalized based on the initial evaluations and endoscopy findings. The patients followed up for 30 days.

Hemodynamic status was classified as stable, intermediate, and unstable based on systolic blood pressure (SBP) and pulse rate (beats/min). SBP <90 mm hg and pulse >110 beats/min was considered unstable, SBP: 90-99 mm/Hg and pulse: 100-110 (beats/min) as intermediate, SBP >100 mm/Hg and Pulse <90 beats/min as stable. Cut-off values for blood pressure and pulse are based on the values determined in GBS, AIMS65, and T-scores (15,16, 20).

Outcomes

The primary outcomes of the presented study were as follows: (1) Need for endoscopic treatment, (2) Hospitalization, (3) Rebleeding, and (4) 30-day mortality. Rebleeding was defined as more than a 2 g/dl decrease in hemoglobin along with signs of bleeding. Rebleeding was confirmed by a second look endoscopy (presence of fresh blood into the stomach or duodenum, active bleeding or SRH), and mortality was defined as any death occurring within 30 days after bleeding.

Patients were divided into low- and high-risk groups. High-risk patients were determined as the presence of one of the following necessities: blood transfusion, surgery, or endoscopic or radiologic interventions to control the bleeding. Conversely, the absence of any interventions mentioned above was determined as low-risk.

Data Collection

In addition to the bleeding-related symptoms (hematemesis, coffee-ground vomit, melaena, syncope), data regarding past medical history, hemodynamic status, and laboratory and endoscopic findings were collected prospectively. Data Hospitalization, blood transfusion, endoscopic treatment, interventional radiology or surgery, rebleeding, and 30-day mortality were registered prospectively using the hospital's electronic civil medical registration system. Patients discharged within 24 hours were followed up with outpatient clinic visits after one week and at the end of the fourth week.

Statistical Analysis

The SPSS 23.0 Statistical Package Program for Windows (SPSS, IBM, Chicago, IL, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to test the normality of distributions. Categorical data are presented as percentages and continuous variables are presented as mean ± standard deviation (SD) for variables with normal distribution or median and interquartile range (IQR) for variables with abnormal distribution. The statistical comparisons of continuous variables were performed using independent samples t-test or Mann-

Whitney U test regarding the distribution pattern. The correlation between score systems and length of stay in the hospital was evaluated using Spearman's test. Receiver operating characteristic (ROC) curves for disease outcomes were calculated to evaluate the detection ability of score systems. The area under the ROC curve (AUC) was used as an overall measure of discrimination. ROC was compared using the De Long test* (Medcalc® Software, Mariakerke, Belgium). A two-tailed p-value of <0.05 was considered statistically significant.

*DeLong ER, DeLong DM, Clarke-Pearson DL (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837–845

RESULTS

Patient Characteristics and Baseline Scores

A total of 578 patients presented to the emergency department with acute UGIB, of whom 109 patients were excluded from the study for the following reasons: 54 patients were acute variceal UGIB, 38 patients were unsuitable for endoscopy due to poor prognosis or refused endoscopy, and 17 patients had missing data. The remaining 469 patients were included in the study (**Figure 1**).

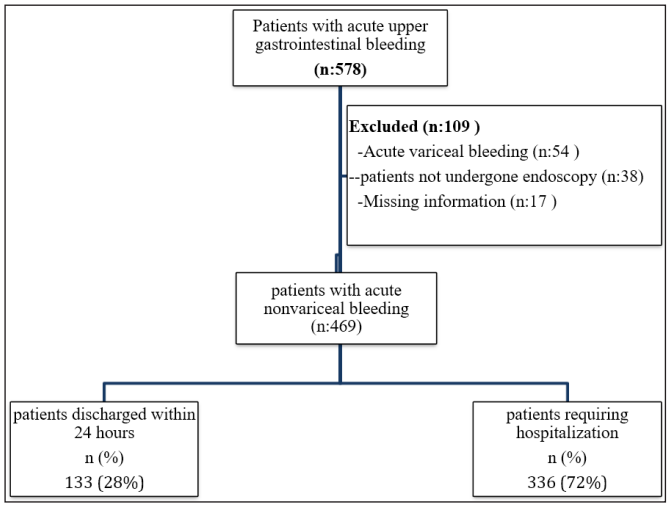

Figure 1. Flowchart of inclusion criteria and followed up hospitalized or outpatients presenting with UGIB.

Patients' characteristics, comorbidities, and endoscopic findings are shown in **Table 1**. The median age was 67.0 (50.5-78.5), and 315 (67%) were male. 239 (51%) of the patients were presented with hematemesis, 319 (68%) with melena, 129 (28%) with melena and hematemesis, and 77 (16%) patients also had hematochezia and/or syncope. While 100 (21%) of the patients had a previous history of UGIB, 16 (3%) had previously undergone gastric surgery. Of the patients with UGIB, 90 (19%) were taking NSAIDs, 139 (30%) patients were antithrombotic and 72 (16%) patients were using anticoagulants.

Table1. Patients' characteristics, comorbidities, medications and endoscopic findings.

	Total (N= 469)
Median age, (years)	67.0 (50.5-78.5)
Gender, (male)	315 (67%)
Presenting symptoms	
Hematemesis	239 (51%)
Melaena	319 (68%)
Hematemesis/melaena	129 (28%)
Comorbidities	
Cardiovascular diseases	101 (22%)
Cerebrovascular diseases	39 (8%)
Chronic renal disease	51 (10%)
Hypertension	209 (45%)
Chronic liver disease	10 (2%)
Malignant diseases	56 (12%)
Previous episode of UGIB	100 (21%)
Previous GIS surgery	16 (3%)
Medication	301 (65%)
NSAIDs	90 (19%)
Antithrombotic agent	
Aspirin	126 (27%)
DAPT	13 (3%)
Anticoagulants	
Warfarin	41 (9%)
NOAC	31 (7%)
Pulse > 100 (beats/min)	198 (42%)
Systolic blood pressure < 90mmHg	34 (7%)
Hemoglobin level on admission (g/dL)	9.9 ± 2.9
BUN level on admission (mg/dl)	71.0 (47.0-113.0)
Endoscopic findings	
Peptic ulcer	
Gastric	77 (16%)
Duodenal	157 (34%)
Erosive esophagitis/ulcer	45(9%)
Upper gastrointestinal malignancy	37 (8%)
Mallory–Weiss syndrome	16 (3%)
Erosive gastropathy/ duodenopathy	73 (16%)
Others (angioectasia, Cameron lesion, dieulafoy lesion, etc.)	43 (9%)
Lesion not visualized	22 (5%)

Results are expressed as: mean + SD or median (IQR) or frequency (%). UGIB: upper gastrointestinal bleeding, GIS: gastrointestinal system, NSAIDs: Non-steroidal anti-inflammatory drugs, NOAC: New generation oral anticoagulant, DAPT: dual antiplatelet therapy, BUN: blood urea nitrogen.

Among the study population, 133 (28%) patients were discharged within 24 hours, while the remaining 336 (72%) patients were hospitalized. The median length of hospital stay was 6.6 (0-8.0) days. Endoscopic treatment was required in 109 (23%), and rebleeding was observed in 36 (8%) patients. The 30-day mortality rate was 11%. Patients' clinical outcomes and scoring systems at admission or after endoscopy are listed in **Table 2**. Median score values evaluated at admission or after endoscopy in patients' clinical RS was 3.0 (1.0-4.0), complete RS was 5.0 (3.0-6.0), GBS was 9.0 (6.0-12.0), AIMS65 score was 1.0 (0-2.0), and T-score was 9.0 (8.0-11.0) (**Table 2**).

Comparison of Scores' Ability to Predict Outcomes

The outcome prediction ability of the scoring systems is listed in **Table 3**. In addition, a comparison was made for the area under the curve for all scoring systems. The ability to predict the need for endoscopic treatment, hospitalization, rebleeding, and mortality in low and high-risk patients according to the cut-off value of all scoring systems is shown in **Table 4**.

Complete Rockall score was superior among all risk scores regarding the prediction of the need for endoscopic treatment (AUC:0.707, %95 CI: 0.663-0.743, for all scores p<0.001) and hospitalization (AUC: 0.678, %95 CI: 0.633-0.720). Regarding the prediction of hospitalization, no difference was found in AUROC between the Complete Rockall score (AUC: 0.678) and GBS (AUC: 0.638). While the AIMS65 score had the highest discriminative ability (AUC: 0.688) at predicting rebleeding compared with the Clinical RS,

Table 2. Patients' clinical outcomes and risk scoring systems at admission or after endoscopy.

	Total (N=469)
Discharged within 24 hours	133 (28%)
Hospitalization	336 (72%)
Clinical hospitalization	239 (51)
Intensive care unit	97 (21)
Length of stay (median)	6.6 (0-8.0)
Need for Endoscopic intervention	109 (23%)
Heater coagulation	25 (5%)
Argon plasma coagulation	9 (2%)
Hemoclips	75 (16%)
Surgery/interventional radiology	8 (2%)
Need transfusion (U)	255 (54%)
Rebleeding (during hospitalization)	36 (8%)
30-day mortality	50 (11%)
Scores	
Clinical Rockall Score	3.0 (1.0-4.0)
Complete Rockall Score	5.0 (3.0-6.0)
Glasgow Blatchford Score	9.0 (6.0-12.0)
AIMS65	1.0 (0-2.0)
T-score	9.0 (8.0-11.0)

Results are expressed as: median (IQR) or frequency (%).

Table 3. Ability of risk scoring systems to predict clinic outcomes.

	AUROC (95% CI)	Complete Rockall P (95% CI)	Glasgow Blatchford P (95% CI)	AIMS65 P (95% CI)	T score P (95% CI)
Need for endoscopic treatment					
Clinical Rockall	0.536 (0.489-0.582)	<0.001 (0.144-0.197)	0.116 (-0.012-0.115)	0.888 (-0.042-0.049)	0.308 (-0.028-0.090)
Complete Rockall	0.707 (0.663-0.748)	-	<0.0001 (0.061-0.178)	<0.001 (0.127-0.221)	<0.001 (0.084-0.195)
Glasgow Blatchford	0.587 (0.541-0.632)	-	-	0.067 (-0.003-0.112)	0.368 (-0.023-0.064)
AIMS65	0.533 (0.486-0.579)	-	-	-	0.262 (-0.025-0.093)
T score	0.567 (0.520-0.612)	-	-	-	-
Hospitalization					
Clinical Rockall	0.589 (0.543-0.634)	<0.001 (0.064-0.113)	0.103 (-0.009-0.107)	0.738 (-0.040-0.056)	0.309 (-0.027-0.086)
Complete Rockall	0.678 (0.633-0.720)	-	0.163 (-0.016-0.096)	0.001 (0.030-0.131)	0.032 (0.005-0.114)
Glasgow Blatchford	0.638 (0.592-0.681)	-	-	0.173 (-0.017-0.098)	0.390 (-0.024-0.062)
AIMS65	0.597 (0.551-0.642)	-	-	-	0.472 (-0.036-0.079)
T score	0.618 (0.573-0.663)	-	-	-	-
Rebleeding					
Clinical Rockall	0.601 (0.555-0.645)	0.221 (-0.020-0.086)	0.581 (-0.077-0.137)	0.023 (0.011-0.163)	0.265 (-0.0.38-0.138)
Complete Rockall	0.634 (0.588-0.678)	-	0.954 (-0.102-0.108)	0.191 (-0.027-0.135)	0.714 (-0.073-0.107)
Glasgow Blatchford	0.631 (0.585-0.675)	-	-	0.254 (-0.041-0.155)	0.651 (-0.066-0.200)
AIMS65	0.688 (0.644-0.730)	-	-	-	0.362 (-0.045-0.125)
T score	0.651 (0.606-0.694)	-	-	-	-
Mortality					
Clinical Rockall	0.706 (0.662-0.747)	0.099 (-0.006-0.078)	0.383 (-0.052-0.135)	0.020 (0.016-0.192)	0.502 (-0.057-0.177)
Complete Rockall	0.742 (0.700-0.781)	-	0.090 (-0.012-0.168)	0.126 (-0.019-0.155)	0.882 (-0.077-0.089)
Glasgow Blatchford	0.664 (0.619-0.707)	-	-	<0.001 (0.065-0.226)	0.025 (0.008-0.134)
AIMS65	0.810 (0.771-0.844)	-	-	-	0.056 (-0.002-0.151)
T score	0.735 (0.693-0.775)	-	-	-	-

Table 4. Ability to Identify low risk and high-risk patients and outcome in prediction of need for endoscopic treatment, need for intervention, hospitalization, re-bleeding and 30-day mortality.

	Risk Scoring system	Cut-off	Patients, n, (%)	Need for endoscopic treatment, n, sensitivity (%) / specifity (%)	Hospitalization, n, sensitivity (%) / specifity (%)	Rebleeding, n, sensitivity (%) / specifity (%)	Mortality, n, sensitivity (%) / specifity (%)
Patients classified as low risk*	Clinical RS	0	83 (18)	21, 15.2 / 81.2	51, 15.2 / 75.9	4, 11.1 / 81.8	0, 0 / 80.2
	Complete RS	≤ 2	83 (18)	4, 2.9 / 76.1	43, 12.8 / 69.9	2, 5.6 / 81.3	1, 2.0 / 80.4
	GBS	≤ 1	26 (6)	3, 7.0 / 95.8	9, 2.7 / 87.2	0, 0 / 94.0	0, 0 / 93.8
	AIMS65	0	181 (39)	48, 34.8 / 59.7	116, 34.5 / 51.1	7, 19.4 / 59.8	3, 6.0 / 57.5
	T score	≥ 10	234 (50)	63, 45.7 / 48.2	157, 46.7 / 42.1	10, 27.8 / 48.3	9, 18.0 / 46.3
Patients classified as high risk*	Clinical RS	≥ 3	292 (62)	87, 63.0 / 38.2	218 64.9 / 35.1	27, 75.0 / 38.8	41, 82.0 / 40.1
	Complete RS	≥ 8	50 (11)	31, 22.5 / 94.2	43, 12.8 / 87.2	8, 22.2 / 90.3	14, 28.0 / 91.4
	GBS	≥ 7	337 (72)	114, 82.6 / 32.7	261 77.7 / 42.9	30, 83.3 / 29.1	48, 92.0 / 30.5
	AIMS65	≥ 2	136 (29)	43, 31.2 / 72.1	109 32.4 / 79.7	21, 58.3 / 73.4	37, 74.0 / 76.4
	T score	≤ 6	25 (5)	9, 6.5 / 95.2	19 5.7 / 95.5	4, 25.0 / 88.7	8, 16.0 / 95.6

(* patients classified as low risk and high risk according to risk scoring system).

Complete RS, GBS, and T score (AUC: 0.601, 0.634, 0.631, 0.651 respectively), there was no difference between all scores the area under the curve. AIMS65 score (AUC: 0.810, %95 CI: 0.771-0.844, p<0.05) was superior to the clinical RS and GBS at predicting 30-day mortality. Nevertheless, there was no difference between the AIMS65 score and the other scores of areas under the curve (p> 0.05) (**Table 3**).

The scores with the highest specificity and sensitivity for the need for endoscopic treatment in low-risk patients were the GBS (95.8%) and the T score (45.7%), respectively. In high-risk patients, the T score had the highest specificity (95.2 %), and the Glasgow Blatchford score had the highest sensitivity (82.6%) (**Table 4**).

The scores with the highest specificity and sensitivity for hospitalization in low-risk patients were GBS (87.2%) and T score (46.7%), respectively. In high-risk patients, the T score had the highest specificity (95.5%), and GBS had the highest sensitivity (77.7%).

The scores with the highest specificity and sensitivity for rebleeding in low-risk patients were GBS (94.0%) and T score (27.8%), respectively. In high-risk patients, Complete RS had the highest specificity (90.3%), and the GBS score had the highest sensitivity (83.3%). The scores with the highest specificity and sensitivity for mortality in low-risk patients were GBS (93.8%) and T score (18%), respectively. In high-risk patients, the T score had the highest specificity (95.6%), and the GBS had the highest sensitivity (92.0%).

DISCUSSION

Risk scoring systems can make it easier for the clinician to identify low- and high-risk patients presenting with UGIB. Risk scoring systems for UGIB are essential for identifying high-risk patients to provide intensive care, along with low-risk patients that can be easily managed on an outpatient basis. Previous studies have demonstrated the predictive values of these scores in terms of the need for interventions, prolonged hospitalization, and mortality (24). The clinical RS, GBS, AIMS65, and T-score are pre-endoscopic risk scores that include only clinical variables (25). These risk scores may determine to need for early endoscopy, the decision of early discharged, rebleeding, and mortality. The Complete RS includes both clinical and endoscopic variables (25,26). Pre-endoscopic and post-endoscopic scores were evaluated to determine the optimal risk scores in patients presenting with UGIB based on associated primary outcomes in the presented study.

We showed that in AUROC analysis, Complete RS had the highest discriminative ability to predict the need for endoscopic treatment. Complete RS may facilitate deciding whether to perform an endoscopy. GBS has been the best scoring system to predict the need for endoscopic treatment in previous studies (15, 25, 27). However, in this study, the Complete RS was superior among all risk scores in predicting of need for endoscopic treatment. We found that the GBS had the highest discriminative ability to predict the need for intervention; GBS appears to be the optimal scoring system for predicting the

need for intervention. These results supported previous studies and the European Society of Gastrointestinal Endoscopy recommended in patients with UGIB use of GBS in the last guideline (15, 32). When GBS score is 0 and 1, it means that the need for intervention is very low and early discharge decision can be made (27,28). The median GBS score in the current study was 9, the study population consisted mostly of high-risk patients, which may explain the low sensitivity of GBS in terms of need for endoscopic intervention.

Many studies have shown that scoring systems are insufficient to predict rebleeding (24, 30, 29). In our study AIMS65 score was best at predicting rebleeding compared with the other scores. This may reflect its ability to predict rebleeding in high-risk patients. Another critical concern is the identification of high-risk patient groups. Based on the AUROC analysis in our study, AIMS65 scored the highest discriminative ability at predicting 30-day mortality, respectively. Most of the patients in our study were in the high-risk patient group, and the ability of the scoring systems to predict mortality was significant. In literature, the mortality risk was considered high when more than two components of AIMS65 were present (16, 32). Hyett et al. (32) have reported the superiority of the AIMS65 score when compared to the GBS in predicting inpatient mortality. AIMS65 score is an acronymic risk score which incorporates albumin level, INR, altered mental status, systolic blood pressure and age >65. The rate of UGIB-related morbidity and mortality increases markedly with age (12, 17-19). Altered mental status, which is the components of the AIMS65 score, is frequently observed in elderly UGIB patients, and the fact that they are over the age of 65 may explain that the AIMS65 score is an optimal risk scoring system in the elderly group. However, we did not find any difference between the ability of the complete RS and T-score to predict 30-day mortality. Tammaro et al. (20) reported that the T-score could predict mortality with an accuracy similar to the GBS, especially when the T-score was six or less. Similarly, the complete RS was more than eight or more (14).

The optimal risk score is to divide patients into low-risk and high-risk groups. In the previous studies, cut-off values were determined for low-risk and low-risk patient groups (26, 33). We used these cut-off values as a basis. We found that the sensitivity of risk scoring systems was insufficient in the low-risk group, while GBS had a specificity of over 85% to evaluate all primary outcomes in low-risk patients. Unlike low-risk patient groups, the predictivity of risk scoring systems was significant in high-risk patients. In high-risk patients, GBS was the best scoring system with sensitivity above 77% to evaluate all primary outcomes. We noticed that while the sensitivity of GBS (score seven or more) was better in the high-risk group, this situation was insufficient for the low-risk group to predict this endpoint. Stanley et al. (25) reported that the sensitivity of GBS was low in the high-risk patient group, and the use of GBS in this group of patients was limited. This may be because most of the patients in their study were low-risk patients, unlike our study. In the present study, the T-score (score of six or less) was the best scoring system with specifications above 95% to predict the need for endoscopic treatment, need for intervention, hospitalization, and 30-day mortality in high-risk patients. The recently described T-score has been shown to have the ability to predict the need for intervention, rebleeding, and mortality (20, 34). GBS and T-score are simple calculable pre-endoscopic scores and may predict worse outcomes in high-risk patients, especially when endoscopy is unavailable.

The study's strength was standardized with high accuracy in calculating risk scoring systems Since it is a single-center prospective design and endoscopy is performed on all patients. The study's weakness was that most patients were in the high-risk patient group, resulting in many critical patients being sent to the hospital as it is a tertiary center. This may be the reason why the sensitivity of scoring systems is inadequate in the low-risk patient group.

CONCLUSION

Calculating Complete Rockall and AIMS65 scores is useful in determining UGIB-related endpoints (need for endoscopy, hospitalization, rebleeding, and mortality). GBS and T score have a higher sensitivity and specificity in detecting high-risk patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Scientific Researches Ethics Committee (Date: 02.09.2020, Decision No: E1/1051/2020).

Informed Consent: Written consent was obtained from the patient participating in this study.

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 patellar tendon morphology in Turkish population: a cross-sectional study

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ABSTRACT

Aim: This study aims to investigate the length, width and thickness of the patellar tendon and the type and length of the patella with MRI and to reveal the normal values of patellar tendon morphology specific to the Turkish population.

Material and Method: The study was conducted with 348 individuals (137 males, 211 females) who applied to our hospital, had no anterior knee pathology, and had knee MRIs. The length, proximal and distal width and thickness of the patellar tendon, patella type, prepatellar and infrapatellar fat pad signal characteristics and Insall-Salvati ratio were evaluated on knee MRI images of these individuals.

Results: Type I patella was detected in 23.9%, type II in 57.2%, type III in 16.1%, and type IV in 2.9% of individuals. The mean length of the patella was 41.26±4.36 mm, the patellar tendon length was 47.36±6.70 mm, the proximal width was 28.86±3.49 mm, the distal width was 23.53±2.69 mm, the proximal thickness was 3,62±1.47 mm, and distal thickness was 5.21±1.1 mm. It was determined that the Insall-Salvati ratio did not cause a statistical difference according to age, but the patella type showed significance with the Insall-Salvati classification.

Conclusion: While evaluating MRI images, the effect of social differences on measurements should not be ignored; normal measurement values of the tendon should be known to evaluate pathological measurements.

Keywords: Patellar tendon, Patella type, Insall-Salvati ratio

INTRODUCTION

Knee stability depends on the mechanical axes of the joint, bony contours, fat pads (infrapatellar and prepatellar), intra-articular stabilizers (meniscus and cruciate ligaments) and extra-articular stabilizers (capsular ligaments, lateral ligaments and musculotendinous units) (1). The patellar tendon is the main component that plays a role in this stabilization. Some of the fibers in the central part of the common tendon of the quadriceps femoris muscle extend to the tibia after its attachment to the patella and form the patellar tendon, and this tendon plays a role in the extension of the knee by transmitting the force created by the quadriceps femoris to the tibia (2). Inflammatory conditions such as patellar tendinopathy, Osgood Schlatter disease, and Sinding Larsen Johansson syndrome can affect the patellar tendon, increasing its thickness.

The patellar tendon is also used as an autograft in anterior cruciate ligament reconstruction operations (3). Due to the fixed length of the patellar tendon, graft-tunnel length mismatch is a common intraoperative technical problem. Too narrow or too long patellar tendon affects the results of this operation negatively. This condition is usually caused by the excessive length of the tendon (4). Since the patellofemoral joint is a complex joint with high functionality and a complex biomechanical structure, patellofemoral joint anatomy is thought to be determinant in problems in the anterior part of the knee. Therefore, diagnosing and treating diseases that cause patellofemoral pain mainly depends on understanding this joint's anatomy and biomechanics. However, studies investigating patellofemoral morphology have generally focused on pathological conditions, infrapatellar (Hoffa's fat pad) impingement syndrome (5, 6) and patellofemoral chondromalacia (2, 7). In all these studies, symptomatic patients were selected, and patellar tendon morphology in healthy individuals was not emphasized. Especially in patients

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whose infrapatellar and prepatellar fat pads have been removed for pathological reasons, the importance of fat pads has been clearly understood by the changes in the mechanics of the knee and the emergence of the effects of friction (8). Therefore, this study also investigated whether the infrapatellar and prepatellar fat pads in healthy individuals were edematous.

Parameters such as a patient's actual patellar tendon length, patella type and diameter constitute anthropometric measurements that are clinically important and can guide racial studies (9, 10). Even the absence of one of these stabilizing factors will impair the normal function of the knee (11, 12). In the researches, it has been determined that the patellar tendon morphology specific to Turkish society has not been determined in detail. Therefore, this study aimed to determine the normal morphology of the patellofemoral junctions and the reference values specific to the Turkish population by MRI. The normal mechanics and stability of the knee occur with the synchronized function of these components. Therefore, knowing the community-specific values of patellar tendon morphology will provide great convenience to Turkish surgeons in today's knee surgery. This study aims to measure the width, thickness, type and length of the patellar tendon with MRI and to reveal the patella type, length and normal values of tendon dimensions.

MATERIAL AND METHOD

Study Design

This study was a retrospective, observational, and single center study conducted between 01.2021 and 01.2023. The study was carried out with the permission of Bayındır Hospital Ethics Committee (Date: 16.02.2023, Decision No: BTEDK-06/23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Excluding criteria: Among the 524 individuals who underwent knee MRI in our center between 01.2021 and 01.2023, 479 individuals over the age of 18 were selected and who had a previous knee operation, fracture, dislocation, osteomyelitis, necrosis, anterior knee pain, apophysitis, mass, patellar tendinopathy were excluded from the study, and 348 patients were included.

Including criteria: Individuals without any symptoms were included in the study. Unilaterally, 348 anterior knee pathologic were evaluated.

Research Parameters

All measurements of patellar tendon dimensions were measured from the localizations specified by Chang et al. (13) and noted.

Patellar type: In this study, patella classification was performed as described by Wiberg (14) and Baumgartl (15). Three different types of the patella were defined by Wiberg (1941), and then Baumgartl (1964) defined type IV as "Jaegerhut" patella, which has no medial face and, therefore, no median protrusion.

Insall–Salvati ratio: Insall–Salvati ratio is the ratio of the patellar tendon to the patellar length in the sagittal plane from the section where the largest width of the patella was measured. Its normal value is between 0.8-1.2. If it is less than 0.8, it is called patella baja; if it is larger than 1.2, it is called patella alta (16).

MRI Protocol

MRI examinations were performed using a 1.5 T scanner (Gyroscan Intera, Philips Medical Systems, Nederland B. V.) with a standard dedicated knee coil. During scanning, the patients were given a supine position with their knees at 0-30 degrees of flexion. The imaging protocol constituted the following five routine sequences: Coronal fast spin-echo T1-weighted, sagittal fat-suppressed proton density-weighted, coronal fat-suppressed proton density-weighted, axial fat-suppressed proton density-weighted and sagittal fast spin-echo T2-weighted. All measurements were made by two radiologists at different times and independently of each other. The study examined intra-observer and inter-observer agreement by calculating Cohen's kappa coefficient and intra-class correlation coefficient. Inter-observer agreement was analyzed as 91%.

Statistical Analysis

The quantitative parameters were measured manually using the Extreme Picture Archiving and Communications System (PACS) system (Ankara, Türkiye) for the study groups. All the measurements were performed on the osseous surfaces. Length measurements are in millimeters (mm). Statistical analyses were carried out using SPSS for Windows statistical package (version 21.0; SPSS, Chicago, Illinois), and a p-value <0.05 was considered statistically significant.

RESULTS

It was determined that 39.7% of the individuals included in the study were male, 60.3% were female, 37.4% were between 18-39, and 42.5% were between 40 and 59. Type I patella was detected in 23.9%, type II in 57.2%, type III in 16.1%, and type IV in 2.9% (Table 1). The Insall-Salvati ratio was found to be patella baja in 1.7% (n=6), normal in 79% (n=275), and patella alta in 19.3% (n=67). Edema in the prepatellar fat pad was diagnosed in 46.3% of the patients, and edema in the infrapatellar fat pad in 15.2% (**Figure 1** and **2**).

Length of the patella, patellar tendon length and proximal diameter were higher in males than females ($p<0.05$). The

mean patellar length was 41.26±4.36 mm, the patellar tendon length was 47.36±6.70 mm, the proximal width was 28.86±3.49 mm, and the distal width was 23.53±2.69 mm. It was determined that distal width, proximal and distal thickness, and Insall-Salvati ratio did not differ according to gender (p>0.05). The mean Insall-Salvati ratio was 1.18±.59 (**Table 2**).

Table 1. Descriptive information of the research

	Frequency	Percent
Sex		
Male	138	39.7
Female	210	60.3
Age		
18-39	130	37.4
40-59	148	42.5
60 and over	70	20.1
Side		
Right	144	41.4
Left	204	58.6
Patellar Type		
Type I	83	23.9
Type II	199	57.2
Type III	56	16.1
Type IV	10	2.9
Prepatellar Fat		
Normal	187	53.7
Edematous	161	46.3
Infrapatellar Fat		
Normal	295	84.8
Edematous	53	15.2
Insall-Salvati Ratio		
Less than 0.8 (Patella baja)	6	1.7
0,8-1,2 (Normal)	275	79.0
Larger than 1.2 (Patella alta)	67	19.3

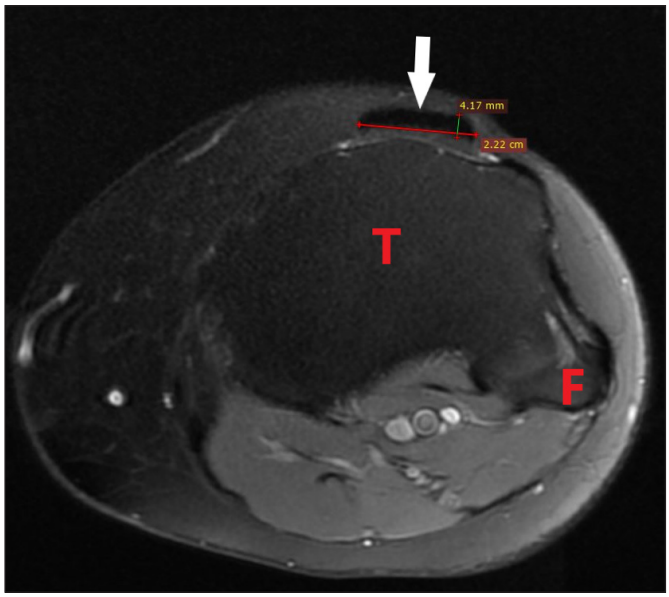

Figure 1: Thickness and diameter measurements of the patellar tendon on transverse MR image (fat-suppressed PD T2A). T: Tibia, F: Fibula, White arrow: patellar tendon (section taken 1 cm from the distal attachment level).

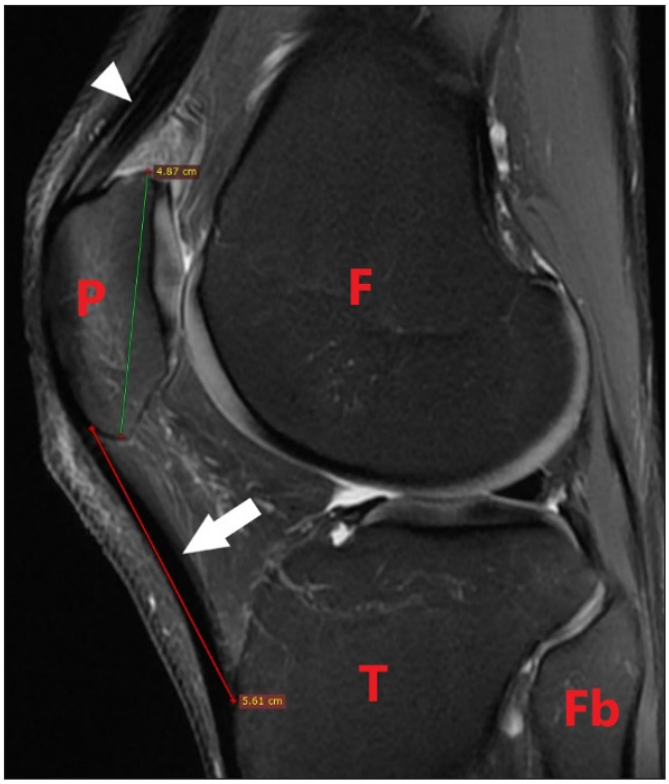

Figure 2: Patella and patellar tendon length measurements on sagittal MR image (fat-suppressed PD T2A). P: Patella, F: Femur, T: Tibia, Fb: Fibula, White arrowhead: quadriceps tendon, White arrow: patellar tendon

Table 2. Distribution of patellar tendon sizes by gender

	Mean±SD	Male (138)	Female (210)	t/p
Length of patella	41.26±4.36	43.89±4.78	39.49±2.86	10.72/.00
Patellar tendon length	47.36±6.70	49.93±6.72	45.63±6.12	6.14/.04
Proximal width	28.86±3.49	30.72±32	27.64±3.09	8.88/.00
Distal width	23.53±2.69	24.96±2.42	22.59±2.44	.01/.90
Proximal thickness	3.62±1.47	3.65±.89	3.59±1.73	1.91/.95
Distal thickness	5.21±1.10	5.48±16	5.03±1.02	1.65/.20
Insall–Salvati ratio	1.18±.59	1.21±.91	1.16±.17	.79/.43

Test: Independent t-test, p<0,05

According to age and Insall-Salvati classification, 74.6% normal, 24.6% patella baja were detected in patients between 18-39 years old, 79.7% normal, 2.7% patella alta in patients between 40-59 years old, and %85.7 normal, 12.9% patella baja in patients older than 60 years (**Figure 3**).

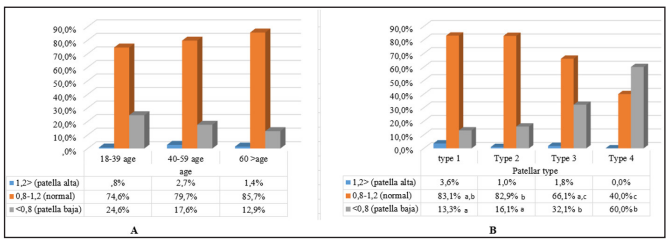

Figure 3. The relation of patella height/position with A-age (p>0.05) and B-patella type (p<0.05) according to the Insall-Salvati index

It was determined that the Insall-Salvati index did not cause a statistical difference according to age. The patella type showed significance with the Insall-Salvati classification (Figure 1). According to the Insall-Salvati index, normal was observed in type I patella with a rate of 83.1%, patella baja was observed in type III patella with the highest rate (60.0%), and patella alta was observed in the highest rate (%3,6) in type I patella (Figure 3).

It was determined that there was a decrease in the Insall-Salvati index with age, but this decrease was not statistically significant between age groups. In addition, it was determined that the Insall-Salvati ratio-infrapatellar fat pad relationship did not differ significantly between normal (1.18±0.63) and edematous (1.17±0.28) individuals. Likewise, the Insall Salvati ratio-prepatellar fat pad relationship was not statistically significant between normal (1.21±0.79) and edematous (1.18±0.16) subjects (p>0.05) (**Figure 4**).

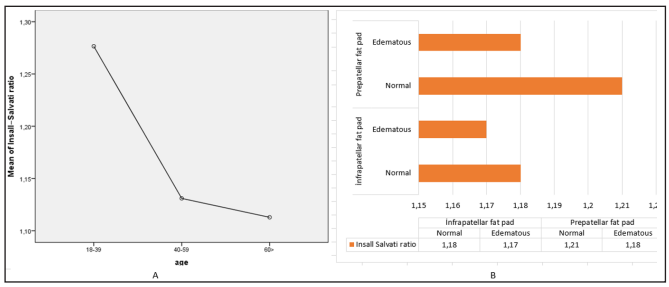

Figure 4. A. Variation of Insall-Salvati ratio by age B. Relationship between the infrapatellar and prepatellar fat pad and Insall-Salvati ratio

DISCUSSION

Lateral knee radiographs, which usually require a specific knee position, have also been used to evaluate patellar height (9). However, measuring patellar tendon length on lateral knee radiography is problematic because it is sometimes difficult to identify the distal attachment point of the tendon in the tibial tubercle due to differences in bone morphology in this region. However, magnetic resonance imaging (MRI) is recognized as a valuable, accurate and reproducible tool for structural joint measurements. In addition, MRI is much more reliable than other invasive methods, as it clearly shows the proximal part of the patellar tendon and allows the entire patellofemoral joint to be shown fully and clearly (10, 11). Various publications in the literature measure the dimensions of the patellar tendon by ultrasonography or MRI images, intraoperatively or in cadaver studies. However, it has been reported in many studies that cadaver and ultrasonographic measurements do not yield real results (17, 18). MRI method has been used with increasing frequency in recent years in imaging of the knee joint due to its possibility of high soft tissue contrast, multiplanar imaging opportunity and no known side effects. Although the structures of the knee joint can be evaluated with ultrasound and computed tomography, the morphology (length, thickness, width, Insall-Salvati ratio, etc.) of the patellar tendon was analyzed with MRI in this study, as it is the gold standard in the evaluation of soft tissues in the knee and provides excellent resolution in soft tissues.

According to our research results, type I patella was detected in 23.9%, type II in 57.2%, type III in 16.1%, and type IV in 2.9% of individuals. The mean length of the patella was 41.26±4.36 mm, the patellar tendon length was 47.36±6.70 mm, the proximal width was 28.86±3.49 mm, the distal width was 23.53±2.69 mm, the proximal thickness was 3,62±1.47 mm, and distal thickness was 5.21±1.1 mm. It was determined that the Insall-Salvati ratio did not cause a statistical difference according to age, but the patella type showed significance with the Insall-Salvati classification. Also, the Insall Salvati ratio-prepatellar fat pad relationship was not statistically significant between normal (1.21±0.79) and edematous (1.18±0.16) subjects.

In evaluating patellar tendon morphology with age, Uçucu (19) stated that men's patellar tendon width, thickness and length were higher than women in all age groups, but there was no difference between ages. Similarly, the literature has reported that men's patellar tendon sizes are generally larger than women's (13, 20). Our study found that the patella and patellar tendon lengths of men were longer than women but did not differ according to age.

Fredberg et al. (20) reported that patellar tendon sizes were higher in males, the mean patellar tendon length was 40.0 mm, and its width was 36.0-35.0 mm at the proximal and distal. Andriakoula et al. (21), in their study on cadavers in the Greek population, reported that the patellar tendon was, on average, 31.9 mm in width at the proximal and 27.4 mm at the distal. Svensson et al. (22) measured the midpoint of the tendon in their MRI study on Swedes and reported the mean width as 28.6 mm. Basso et al. (17) reported that the mean proximal width of the patellar tendon is 31.2 mm, and its width decreases towards the distal. In addition, the finding that the patellar tendon is thinnest in the middle part suggests that the width in the middle part is an adequate reference for defining the very narrow tendon. Chang et al. (13) stated in their intraoperative research that a tendon width of <27 mm is insufficient for load bearing and renders it inadequate for graft. The findings of Chang et al. (13) on length (40.2 mm) suggest that Korean patients have a shorter patellar tendon. Shaffer et al. (9) reported the mean patellar tendon length as 48.4 mm (range, 40-63 mm). Andriakoula et al. (21) and Peace et al. (18) reported patellar tendon thickness and length as 3.7 mm-43.0 mm and 3.7 mm-42.6 mm, respectively. Uçucu (19) reported the mean patellar tendon length as 42.09±4.88

mm, proximal and distal width as 27.06-28.80 mm, and thickness as 3.88-4.50 mm. In parallel with Uçucu's (19) research results, in our study, the mean length of the patellar was 41.26±4.36 mm, the patellar tendon length was 47.36±6.70 mm, the proximal width was 28.86±3.49 mm, and distal width was 23.53±2.69 mm. Proximal and distal thicknesses were measured as 3.62±1.47 mm and 5.21±1.10 mm, respectively. Pathologically long/short or thicker than normal patellar tendon will directly affect knee joint surgery. In addition, edema and thickening of the anterior suprapatellar fat pad from any cause may affect the patellar tendon. It has even been stated that the thickening of the patellar tendon may increase inflammation in the anterior suprapatellar fat pad with the effect of friction and cause the problem to become chronic (5). In summary, it is thought that patellar tendon sizes for patellofemoral region surgery may differ between populations, and racial differences should be considered before surgical approaches.

It is stated that the patella type can explain the etiology of joint diseases such as knee pain, chondromalacia patella and lateral compression syndrome (16, 19). Wiberg et al. (14), in their prospective study on lateral radiographs, reported that type II and III patella types might be included in the differential diagnosis of patellar pain. Arslan et al. (23) found the incidence of patella types in their anatomical study to be 57% for type II patella, 24% for type I, and 19% for type III. A study performed on Merchant radiographs in Turkish society reported that type I patella was 24%, type II patella 70% and type III patella 6%, and type IV patella was not found in any patient (24). In our study, type I patella was detected in 23.9%, type II in 57.2%, type III in 16.1%, and type IV in 2.9% of individuals. Consistent with the literature, type II patella was primarily detected. Considering that the stress on the patella determines the shape of the patella, type III and type IV patella occur due to the lateral shift of the patella in the sulcus, and there is a symmetrical load on the type I patella.

The position of the patella in the vertical plane is determined by the Insall-Salvati index. The normal value for this ratio is 1±0.2. Below 0.8 is called the inferior patella (patella baja), and above 1.2 is called the patella alta. Patella alta is a good indicator of patellar instability. In this case, the time for the higher-placed patella to reach the femur in flexion increases, and accordingly, excessive lateral movement of the patella may develop (25). In mechanical model experiments, it has been shown that the patella alta causes a decrease in patellofemoral joint contact and an abnormal increase in the surface force between the patella and trochlea (26). Subhawong et al. (27) reported in a recent study that there is a close relationship between edema in the superolateral corner of Hoffa's fat pad and increased patellar tendon-patella length ratio. Kalichman et al. (28) found in their MRI study that an increased Insall-Salvati ratio may cause a tendency to chondromalacia in the patellofemoral joint. While Ergun (29) reported that the Insall-Salvati ratio was higher in women than in men and older people compared to young people, there was no significant difference between gender and age in our study. Our study determined that distal width, proximal and distal thickness and Insall-Salvati ratio did not differ according to gender ($p>0.05$). The mean Insall-Salvati ratio was found to be 1.18±.59. Ergun (29) reported that the Insall-Salvati index was measured as 0.99±0.09 and 0.94±0.1 mm on average in women and men, respectively, and that there was a statistically significant difference between them, and that the Insall-Salvati index increased with increasing age. We found that the Insall-Salvati index decreased with increasing age, but this decrease did not create a statistical difference. We determined that the Insall-Salvati ratio was normal in 79.0% of the individuals in our research group and high in 19.3%. In patients with a high Insall-Salvati ratio, the patellar tendon is stretched during knee flexion and the underlying structures are compressed.

Widjajahakim et al. (4) reported that there is a significant correlation between infrapatellar (Hoffa) fat pad edema and Insall-Salvati ratio in patellar tendon/femur lateral condyle friction syndrome, and an increase in fat pad edema may occur as the ratio increases. Subhawong et al. (27) stated that a high patella causes more tension in the patellar tendon during knee movements, which can easily cause pressure on the bursa between the lateral femoral condyle. In this case, inflammation may develop in Hoffa, leading to edema and pain. The 2004 National Joint Registry report for England and Wales showed that surgeons differ in managing the infrapatellar fat pad during primary knee arthroplasty, with 27% complete removal, 59% partial removal, and 14% non-removal (31). It has been shown that complete infrapatellar fat pad excision can devascularize the patella by interrupting the infrapatellar anastomosis. This anastomosis is important as it also feeds the patellar tendon. In our study, edema in the prepatellar fat pad was diagnosed in 46.3% of the patients and the infrapatellar fat pad in 15.2%, but there was no statistical relationship between the Insall-Salvati ratio and the edema in the fat pads.

Limitations

The Insall-Salvati ratio is the most commonly used patellar height measurement method. However, this method has some disadvantages. One of these is an incorrect ratio measurement due to variations in patellar morphology. We used only the Insall-Salvati ratio in our research, but the patella height can be measured with the modified Insall-Salvati ratio, Caton-Deschamps and Blackburne-Peel ratios.

CONCLUSION

This study reveals the patellar tendon dimensions, both descriptively and surgically, and the clinical and social value of MRI evaluations in healthy individuals in Turkish society. However, it does not contain direct evidence that this potential value was realized in a clinical series. In order to test the clinical value, correlation studies can be done by comparing different patient groups in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bayındır Hospital Ethics Committee (Date: 16.02.2023, Decision No: BTEDK-06/23).

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 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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Increased acute invasive fungal rhinosinusitis in COVID-19 patients

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ABSTRACT

Aim: Acute invasive fungal rhinosinusitis (AIFRS) is a rare infection of the nose and paranasal sinuses that can be fatal. Infection may lead to tissue infarction, necrosis, and thrombosis and rapidly spread intracranially. The aim of this study is to highlight the increasing cases of AIFRS after covid-19 and to investigate the parameters affecting mortality.

Material and Method: Total 11 patients diagnosed with AIFRS after COVID-19 were included in this study. Patient age, gender, comorbid diseases, initial symptoms, time between COVID-19 diagnosis and AIFRS diagnosis, intensive care hospitalization history, medical treatments, surgical findings, antifungal treatment, fungal species grown in culture, mortality, and the relationships of these parameters with mortality were also evaluated.

Results: A total of 11 patients diagnosed with AIFRS after COVID-19 were included in the study. Among these patients, 81.8% were male, 18. 2% were female, and ages ranged from 57 years to 89 years. The mean time between COVID-19 infection and development of IFRS in patients was 26.09±18.04 days. The initial symptoms in 45.45% of the patients were unilateral periorbital edema, vision loss, and total ophthalmoplegia. The surgical approach was purely endoscopic in all patients. In our study, the mortality rate was 72.7% in COVID-19 related AIFRS patients.

Conclusion: As a result, in our study, we found an increase in AIFRS incidence and mortality due to the systemic effects of COVID 19 and the treatments used for it. AIFRS should be suspected when a patient presents acute sinusitis symptoms after COVID-19 infection.

Keywords: COVID-19, *Mucor*, AIFRS, ophtalmoplegia

INTRODUCTION

Acute invasive fungal rhinosinusitis (AIFRS) is a rare infection of the nose and paranasal sinuses that can be fatal. Infection may lead to tissue infarction, necrosis, and thrombosis and rapidly spread intracranially, resulting in fungemia and death; indeed, the mortality rates of AIFRS infection reported in the literature are between 40% and 80% in the studies of Chang et al. (1), Shanbag et al. (2), Fadda et al. (3), Ergun et al. (4).

Although many fungi can be causative agents of AIFRS, the most commonly isolated fungi are *Aspergillus* spp. (mainly *A. fumigatus* and *A. flavus*) and Zygomycetes (*Mucor*, *Rhizopus*, and *Absidia*); Singh et al. (5), Montone et al. (6).

AIFRS is caused by opportunistic pathogens that typically develop in immunocompromised patients, such as those with hematologic malignancies, acquired immunodeficiency syndrome, neutropenia, or diabetes; those receiving bone marrow or organ transplant; or those on long-term steroids; Ryu et al. (7), Fernandez et al. (8), Wu et al. (9).

Patients with AIFRS present with fever and localized symptoms, the most common of which include facial swelling, nasal congestion, headache not responding to analgesics, ophthalmoplegia, proptosis, cranial nerve palsies, and vision disturbances or loss. Although early diagnosis can be achieved with the presence of predisposing factors in the patient and the support of clinical and radiological findings, microscopic examination and histopathological evaluation remain necessary to obtain a definitive diagnosis of AIFRS.

Severe COVID-19 is associated with immune dysregulation and may be associated with a wide range of bacterial and fungal co-infections. The literature reports several cases of invasive fungal infections, especially

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invasive pulmonary aspergillosis, after COVID-19 infection. However, limited studies on the development of IFRS in COVID-19 patients are available. The aim of this study is to investigate and report the clinical findings, diagnosis, treatment processes, and mortality and morbidity rates of AIFRS patients with COVID-19 infection during the pandemic to assist in early diagnosis and treatment development.

MATERIAL AND METHOD

A retrospective study was conducted on AIFRS patients with COVID-19 (2020–2021) who had sought treatment at the Ear, Nose, and Throat Department of University of Health Sciences Kayseri City Training and Research Hospital. The study was initiated with the approval by the University of Health Sciences Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15/04/2021, Decision No: 373). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Total 11 patients diagnosed with IFRS after COVID-19 were included in this study. The diagnosis of all patients was achieved by mycological or direct examination or culture of biopsy materials. All patients were preoperatively evaluated by endoscopic examination and paranasal sinus computerised tomography (CT). Patient age, gender, comorbid diseases, initial symptoms, time between COVID-19 diagnosis and IFRS diagnosis, intensive care hospitalization history, medical treatments (e.g., steroidal and immunosuppressant treatments for COVID-19), surgical findings, antifungal treatment, fungal species grown in culture, mortality, and the relationships of these parameters with mortality were also evaluated.

The data were analyzed using the SPSS software package. Numbers and percentages were used when defining categorical variables, and mean±standard deviation (min–max) values were used when defining continuous variables. The Wilcoxon signed-rank test was used for dependent-group comparisons, and the Mann–Whitney U test was used for independent-group comparisons. Spearman correlation analysis was used to measure the relationship between variables; $p \leq 0.05$ was considered significant.

RESULTS

A total of 11 patients diagnosed with IFRS after COVID-19 were included in the study. Among these patients, 81.8% were male (n=9), 18. 2% were female (n=2), and ages ranged from 57 years to 89 years (mean=73.73±9.10 years).

Diabetes mellitus (DM) was recorded in 9.09% of the patients (n=1), DM and hypertension(HT) were recorded in 18.18% (n=2); and DM, atrial fibrillation, and hypothyroidism were recorded in 9.09% (n=1). Moreover, 9.09% (n=1) had DM and chronic renal failure (CRF); 9.09% had (n=1) DM, coronary artery disease, Parkinson's disease; 9.09% (n=1) had coronary artery disease, HT, asthma, hyperlipidemia, and previous ischemic cerebrovascular disease; 9.09% (n=1) had DM, HT, and CRF; and 9.09% (n=1) had DM, HT, and cerebrovascular disease. Finally, 9.09% of the patients (n=1) had coronary artery disease and HT, while 9.09% (n=1) had DM and thalassemia carriage (**Table 1**).

Table 1. Distribution of patients according to sociodemographic and clinical characteristics

Variables	Number (%)	Mean± standard deviation (min, max)
Age (year)	11 (100%)	73,73±9,10 (57-89)
Male (n)	9 (18.2%)	
Female (n)	2 (76.5%)	
DM (n)	1 (9.09%)	
DM+HT (n)	2 (18.18%)	
DM+AF+Hypo-thyroidism (n)	1 (9.09%)	
DM+CRF (n)	1 (9.09%)	
DM+ CAD+ Parkinson's disease (n)	1 (9.09%)	
CAD+HT+asthma, hyperlipidemia, and previous ischemic cerebrovascular disease (n)	1 (9.09%)	
DM+HT+CRF (n)	1 (9.09%)	
DM+HT+CVH (n)	1 (9.09%)	
KAH+HT (n)	1 (9.09%)	
DM+thalassemia carrier (n)	1 (9.09%)	

The mean time between COVID-19 infection and development of IFRS in patients was 26.09±18.04 days (min=8 days; max=75 days). The initial symptoms in 45.45% of the patients (n=5) were unilateral periorbital edema, vision loss, and total ophthalmoplegia. In addition, 9.09% of the infected patients (n=1) had right facial swelling and fever, 9.09% (n=1) had abscess and endophthalmitis in the left buccal region, 9.09% (n=1) had soft tissue swelling in the left premaxillary region, 9.09% (n=1) had right facial numbness and pain, and 9.09% (n=1) had periorbital edema only. Pain in the right half of the face was reported by 9.09% (n=1) of the patients. Among the patients, 9.10% (n=1) remained in the intensive care unit for 4 days before the development of IFRS. Steroid treatment was applied to 90.90% of the patients. The steroid history of one patient was not known. Two of the three patients (66.66%) administered immunosuppressant treatment remained alive, while all other patients died (**Table 2**).

Table 2. Distribution of patients according to initial symptoms of invasive fungal rhinosinusitis

Variables	Number (%)
Unilateral periorbital edema, visual loss and total ophthalmoplegia	5 (45.45%)
Right facial swelling and fever	1 (9.09%)
Abscess and endophthalmitis in the left buccal region	1 (9.09%)
Soft tissue swelling in the left premaxillary region	1 (9.09%)
Right face numbness and pain	1 (9.09%)
Periorbital edema	1 (9.09%)
Pain in the right half of the face	1 (9.09%)

No significant correlation was found between age and time elapsed between COVID-19 infection and the development of IFRS (p=0.840; r=−0.069), between age and survival after the development of IFRS (p=0.119; r=−0.498), or between the lifespan of eight patients who died and the time elapsed between COVID-19 infection and the development of IFRS (p=0.012; r=0.977). After the development of IFR, no significant correlation between age and the survival of eight patients who died (p=0.037; r=0.931) was noted. Considering the life span of all patients from the development of IFRS to today, no significant correlation between life span and the time between COVID-19 infection and the development of IFRS (p=0.979, r=0.009) was found (**Table 3**).

Table 3. Correlations of various variables in patients included in the study (*p≤0.05 was considered significant)

Variable	p and r value	
	p value	r value
Age - time between COVID-19 and IFRS	0.840	-0.069
Age-life expectancy after IFRS	0.119	-0.498
Life expectancy after IFRS-time between COVID-19 and IFRS	0.979	0.009
Duration of steroid use-life expectancy after IFRS	0.355	0.309
Duration of steroid use time between COVID-19 and IFRS	0.498	-0.229

When life expectancy after the development of IFRS was examined by gender, no significant difference was found between genders (p=0.334). No significant difference in terms of the time elapsed between the development of COVID-19 infection and IFRS was found between genders (p=0.813). The mean duration of steroid use was 12.73±5.08 days. No significant difference in terms of survival after the development of IFRS and the time elapsed between COVID-19 infection and the development of IFRS was found between patients using decort or prednol (p=0.334 and p=0.748, respectively; **Table 4**). No significant correlation between the duration of steroid use of the patients and the life span after the development of IFRS and between the duration of steroid use and the time between COVID infection and the development of IFRS was noted (p=0.355, r=0.309 and p=0.498, r=−0.229, respectively; **Table 3**). No significant difference in terms of survival after the development of IFRS and time elapsed between COVID infection and the development of IFRS was found between the groups using and not using immunosuppressants (p=0.065 and p=0.539, respectively; **Table 4**).

Table 4. Distribution of life expectancy and time elapsed between COVID-19 and ifrs development according to various variables (*p≤0.05 was considered significant).

Variables	Life expectancy after IFRS	p value	Time between COVID and IFRS	p value
Gender		0.334		0.813
Female	82.50±95.45		20.50±0.70	
Male	58.22±81.49		27.33±19.93	
Use of steroids		0.334		0.748
Dexamethasone	67.25±65.66		24.50±7.23	
Prednisolone	67.50±97.75		28.17±24.60	
Use of immuno- suppressants		0.065		0.539
Used	131±108.67		33±36.59	
Did not use	37±53.86		23.50±7.38	

In our examination findings, periorbital swelling, redness, exophthalmos and chemosis were the most common findings in patients presenting with eye involvement (**Figure 1**). In our endoscopic examination findings, most of the patients had widespread drying, discoloration in the middle turbinate (blackening), and purulent discharge in the middle meatus. Fungal hyphae were also seen on the middle turbinate in some of the patients (**Figure 2**).

Figure 1. IFRS patient with total ophthalmoplegia

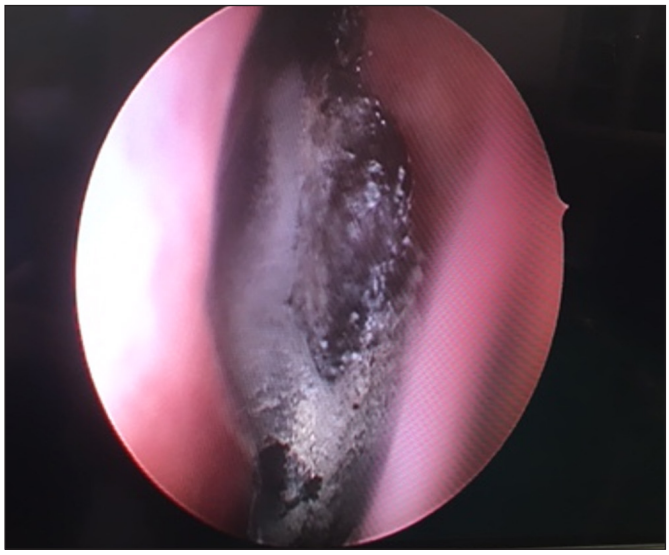

Figure 2. Necrotic middle turbinate and overlying fungal hyphae

Fungal hyphae were visible in the microscopic examination of the biopsy materials of all patients (**Figure 3**). *Mucor* grew in the fungal culture of most of the patients (n=10) (**Figure 4**), while *Exophiala* spp. grew in the culture of only one patient.

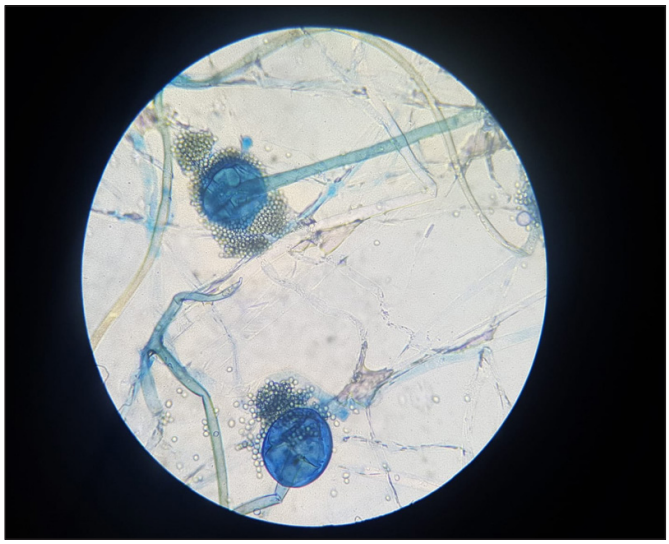

Figure 3. Microscopic image of fungal hyphae

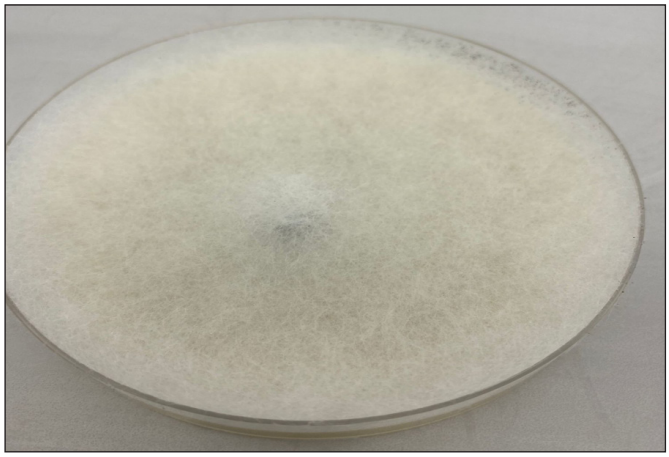

Figure 4. Petri image of fungal hyphae

The surgical approach was purely endoscopic in all patients. Endoscopic debridement, including resection of the middle turbinate, wide middle meatal antrostomy, ethmoidectomy, nasal septectomy, and sphenoidotomy, was performed according to the involved sinuses. Repetitive endoscopic debridement was performed in all patients.

Amphotericin b treatment was given to all patients during their hospitalization, and oral posaconazole was given as maintenance therapy to patients who were successfully discharged.

DISCUSSION

Recent studies have reported that COVID-19 causes superinfections by affecting the immune system and exacerbating the effects of treatments used for the disease; Musuuza et al. (10), Feldman et al. (11). Thus, the occurrence of invasive fungal infections after COVID-19 has drawn increased research attention. Although the most common type of infection recorded in the literature is invasive pulmonary fungal infection, some cases of IFRS have also been reported; Mekonnen et al. (12), Waizel-Haiat et al. (13), Turbin et al. (14). One study indicated that IFRS in post-COVID-19 patients is a new clinical condition; El-Kholy et al. (15). Similarly, we believe that IFRS after COVID-19 infection represents a new clinical situation on account of our multiple experiences of IFRS detected post-COVID over a short period of approximately 8 months. Specifically, over this period, we detected 11 IFRS cases in post-COVID-19 patients but diagnosed only 1 non-COVID-related IFRS case. Thus, COVID-19 may be inferred to increase the frequency of IFRS considerably; however, newer and larger studies are necessary to confirm this supposition.

The mean age of presentation of the patients was 73.73±9.10 years. Although no report on differences in AIFRS infection between males and females has been published, the majority of our patients were male (9 males, 2 females).

All of the patients had comorbidities, the most common of which were diabetes mellitus (81%), hypertension (54%), chronic kidney disease (18%), coronary artery disease (18%), and cerebrovascular disease (18%); one patient was a thalassemia carrier. Most of the patients had controlled diabetes, and none had a history of ketoacidosis. None of our patients had a history of hematological disease or bone marrow and organ transplantation, which are among the most common comorbidities described in the literature; Jestin et al. (16), Pan et al. (17). These findings lead us to believe that COVID-19 may be the main cause of the development of AIFRS in these patients.

While all patients received steroid therapy following their diagnosis with AIFRS, none of them received long-term or high-dose therapy (3 patients, 40 mg/day prednisolone for 14 days; 1 patient, 10 mg/day prednisolone for 14 days; 6 patients, 8 mg/day dexamethasone for 14 days; 1 patient, 8 mg/day dexamethasone for 5 days). Steroids are believed to be highly likely to play a role in the development of AIFRS because of their detrimental effects on the immune system. However, few cases of *Mucor* infection while on systemic steroids has been reported in the literature; Pan et al. (17), Najafi et al. (18). To the best of our knowledge, no study showing that steroid use causes the development of AIFRS is yet available. In fact, we feel that a low dose and short duration of steroid use decreases the likelihood of treatment exerting any effect on the development of AIFRS in these cases.

Most of the patients presented symptoms such pain in the face and cheek (45.45%, five patients) and periorbital edema and vision loss (45.45%, five patients). Other symptoms included facial swelling (three patients). The symptoms reported are similar to those in the literature; Raizada et al. (19), Abdollahi et al. (20).

The time of first diagnosis of COVID-19 and AIFRS was between 8 and 75 days (average, 26.09±18.04 days). If the one patient who developed IFRS on the 75th day was excluded from the analysis, most of the patients demonstrated improvements in AIFRS symptoms within 2–4 weeks. A recently published study indicated that the development of AIFRS after COVID-19 could occur in the early post-COVID period (17.82±2.97 days after a negative result), except in two patients who developed AIFRS while actively infected with COVID-19, similar to our findings; El-Kholy et al. (15).

The literature indicates AIFRS mortality rates of 40%–80%. In our study, the mortality rate was 72.7%, which is close to the upper limit of mortality rates reported in previous studies. However, in these studies, the mortality rate of AIFRS after COVID-19 did not significantly differ from that of infection after other diseases; El-Kholy et al. (15), Ismaiel et al. (21).

CONCLUSION

AIFRS should be suspected when a patient presents acute sinusitis symptoms after COVID-19 infection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15/04/2021, Decision No: 373).

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 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 thoracic CT findings and C-reactive protein and ferritin levels in COVID-19 patients

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ABSTRACT

Aim: In this study, we aimed to establish the relationship between thoracic computed tomography (CT) findings at initial presentation and CRP and ferritin levels in 232 patients diagnosed with COVID-19.

Material and Method: 232 patients who were diagnosed with COVID-19 and underwent a thoracic CT examination at our hospital between Apr 2020 and Aug 2021 were enrolled in this study. The study group was selected from among individuals aged 18-45 years without any chronic diseases and comorbidities. The patients' complaints, RT-PCR test results and blood biochemistry values from the medical records system, and CT imaging from the PACS system were reviewed retrospectively. Parenchymal lesions, ground-glass area, consolidation and combination of ground-glass area and consolidation observed on thoracic CT were considered typical findings. Blood samples were analyzed in the laboratory using standard methods. Routine blood tests were performed to measure serum C-reactive protein and ferritin levels.

Results: Out of the 232 patients infected with COVID-19, 118 were female and 114 were male. While the mean age of all patients was 34.9, the mean ages of men and women were 34.9 and 35.2, respectively. No significant differences were observed between the ages of patients with and without lung involvement (32.9, 37.9, p=0.903, respectively). CT scan showed typical parenchymal findings in 140 patients out of whom 65 were male and 75 were female. With regard to the morphologic features observed on CT, ground-glass density was the most common (74 patients), followed by a combination of ground-glass density and consolidation (34 patients) and finally consolidation (32 patients). In statistical analysis, no significant differences were found in CRP values between patients with and without lung involvement, whereas a significant difference was noted in ferritin values (p=0.196 and p<0.001, respectively).

Conclusion: We examined the relationship between serum CRP and ferritin levels and lung involvement and established that there is a strong correlation between serum ferritin levels and lung involvement. Considering the radiation exposure caused by CT scans as well as the cost of the procedure, we are convinced that serum ferritin levels may help clinicians in terms of early diagnosis, especially in patients with suspected lung involvement.

Keywords: Thoracic CT, COVID-19, ferritin, ground glass areas, consolidation

INTRODUCTION

Coronavirus disease-19 (COVID-19) is an infectious disease primarily involving the respiratory system that has first emerged in Wuhan, China (1). Following droplet transmission from person to person, a person can become infected via the contact of the virus with the mucosa. The most important clinical findings include infection symptoms such as fever, cough and myalgia (2). The disease, which is asymptomatic for the most part, may result in viral pneumonia, sepsis and even death (3,4). COVID-19 is diagnosed by direct detection of viral genomes in RT-PCR in upper respiratory tract samples. Although RT-PCR is considered as the best technique in diagnosing the disease, radiologic imaging started to be used more frequently due to false negative results and prolonged test result process brought about the former. In particular, CT with a sensitivity of up to 98% can help diagnose the disease on the basis of some parenchymal findings in the early stage even in asymptomatic patients (5,6). However, CT should not be used as a screening method due to ionizing radiation (7).

Typical findings such as peripherally located ground-glass areas, consolidation, reticular pattern, septal thickening and nodules as well as atypical findings such as lymphadenopathy, pleural and pericardial effusion in the lung parenchyma may be observed during thoracic BT examination (8,9). Although COVID-19 often remains

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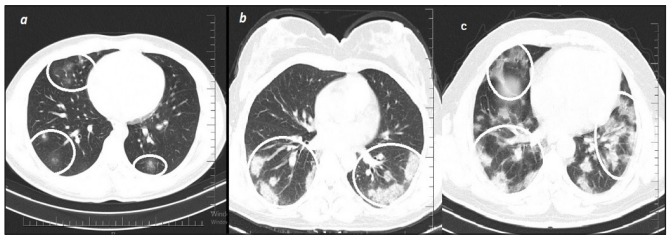
localized and progresses only as a respiratory tract infection, it can sometimes transform into a widespread systemic form involving immunological and inflammatory processes (10). Several biomarkers are required to identify low, intermediate, and high-risk groups in diagnosed patients. Biomarkers measured in laboratory settings are helpful for prognosis and the prevention of serious complications. Studies have shown that elevated serum ferritin, CRP, lactate dehydrogenase, d-dimer, prothrombin time(PT) and IL-6 levels increase the risk of morbidity and mortality (9,11,12).

This article aims to determine the relationship between ferritin and CRP (C-reactive protein) values in COVID-19 patients with lung involvement by using thoracic computed tomography (CT) findings.

MATERIAL AND METHOD

232 patients who were diagnosed with COVID-19 and underwent a thoracic CT examination at our hospital between Apr 2020 and Aug 2021 were enrolled in this study. The study group was selected from among individuals aged 18-45 years without any chronic diseases and comorbidities. The patients' complaints, RT-PCR test results and blood biochemistry values from the medical records system and CT image from the PACS system were retrospectively reviewed. Patients with a history of drug use and active drug use were excluded from the study.

Thoracic CT images of all patients diagnosed with COVID-19 on the basis of clinical examination, laboratory tests and RT-PCR test results were analyzed. All thoracic CT scans were performed in accordance with the appropriate thoracic protocol with a 16-slice CT device (Siemens Scope 16) in the form of axial slices with a thickness of 3 mm and without contrast enhancement. Thoracic CT images were analyzed and recorded at the workstation along with demographic characteristics such as age and gender. Parenchymal lesions, ground-glass area, consolidation and combination of ground-glass area and consolidation observed on thoracic CT were considered typical findings (**Picture**). Patients with atypical findings such as pleural effusion, septal thickening, air bronchogram and mediastinal LAP without any concomitant typical findings were excluded.



Picture. Typical morphologic findings on CT thoracic imaging in patients diagnosed with COVID-19 are shown with a circle; a) ground glass densities b) consolidation c) combination of ground glass densities and consolidation

Blood samples were analyzed in the laboratory using standard methods. Routine blood tests were performed to measure serum CRP and ferritin levels.

Statistical Analysis

SPSS 18.0 software was used for data analysis (Statistical Package for the Social Sciences, Chicago, IL). Comparison of constant variables among independent groups was carried out by using Student's t-test and Mann-Whitney-U test. Categorical values were compared with the Chi-square test. . The relationship of categorical variables with each other was examined with the Pearson's correlation coefficient. The level of significance for statistical results was considered $p<0.05$.

Moreover, the Receiver-operating-characteristic (ROC) curve analysis test was used to establish the diagnostic value of ferritin. The area under the curve (AUC), cut-off, sensitivity and specificity values were established for predicting different models.

RESULTS

Out of the 232 patients diagnosed with COVID-19, 118 were female and 114 were male. While the mean age of all patients was 34.9, the mean ages of men and women were 34.9 and 35.2, respectively. No significant differences were observed between the ages of patients with and without lung involvement (32.9, 37.9, p=0.903, respectively). CT scan showed typical parenchymal findings in 140 patients out of whom 65 were male and 75 were female (**Table**). With regard to the morphologic features observed on CT, ground-glass density was the most common (74 patients), followed by a combination of ground-glass density and consolidation (34 patients) and finally consolidation (32 patients).

Table. Distribution of general characteristics of patients diagnosed with COVID-19

	BT(-)	BT(+)	All patients
No. of patients	92	140	232
Male	49	65	114
Female	43	75	118
Age*	37.9	32.9	34.9
Male	32.4	36.4	34.7
Female	33.5	36.1	35.2
Ferritin ml/ng *	85.7	197.9	153.4
Male	84.2	220.1	161.7
Female	87.3	178.7	145.4
CRP mg/L *	22.7	29.7	26.5
Male	25.1	33.3	29.8
Female	20.1	26.5	24.1

Note: * = mean value

The mean CRP and ferritin values were 26.5 mg/L and 153.4 ml/ng, respectively, in all patients, and 29.7 mg/L and 197.9 ml/ng in patients with lung involvement and 22.7 mg/L and 85.7 ml/ng in patients without lung

involvement. Pearson correlation analysis revealed a significant and positive correlation between CRP and ferritin, r= .160, p< .005 (**Figure 1**).

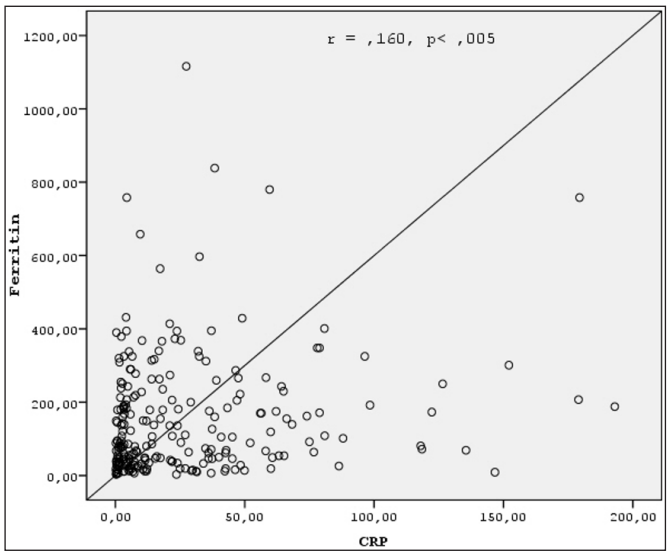


Figure 1. Correlation between serum ferritin and CRP values in COVID-19 patients.

Patients with lung involvement were divided into 3 groups on the basis of CT findings. Group 1 included patients with only ground glass areas while group 2 included patients with only consolidation and group 3 included patients with both ground glass areas and consolidation. In statistical analysis, no significant differences were found in CRP values between patients with and without lung involvement, whereas a significant difference was noted in ferritin values (p=0.196 and p<0.001, respectively) (**Figure 2**). There were no significant individual differences between CRP and ferritin values in the patient groups with involvement (CRP; group 1-2 p=.324, group 1-3 p=.933, group 2-3 p=.420 ferritin; group 1-2 p=.174, group 1-3 p=.785, group 2-3 p=.332).

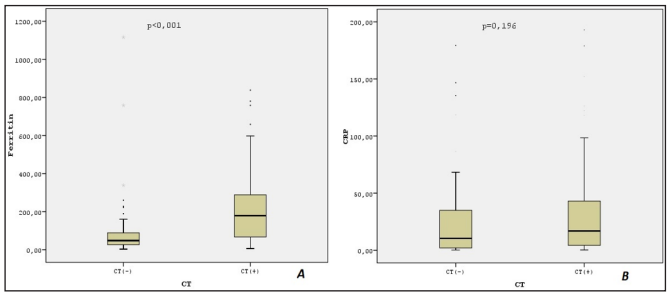


Figure 2. Box plots A and B show the relationship between ferritin and CRP serum values and lung involvement on thoracic CT in COVID-19 patients. The horizontal lines inside each box represent the mean values while the bottom and top rows of each box represent the minimum and maximum values respectively.

In the Receiver operating characteristics (ROC) curve analysis test of ferritin serum value, the AUC value was 0.767 at 95% confidence interval and thus considered to be statistically significant, p<0.001 (**Figure 3**). We established the optimal diagnostic accuracy at selected values for the best odds ratio.

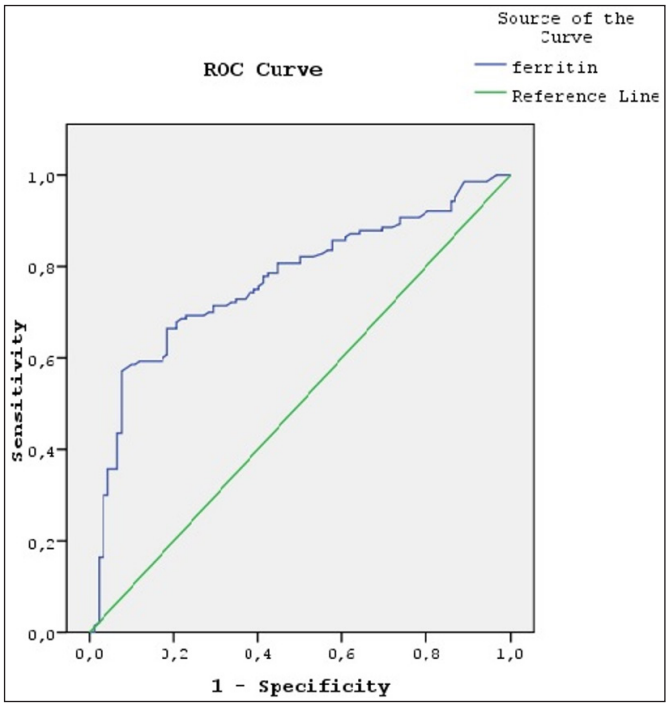


Figure 3. Receiver operating characteristics (ROC) curve analysis of serum ferritin value in the diagnosis of COVID-19.

DISCUSSION

COVID-19 is a usually asymptomatic viral infection that is transmitted primarily through the respiratory system. It may lead to organ damage or even mortality in case of lung involvement. Although RT-PCR test is the best diagnostic method, radiologic imaging is required in some cases as the former is time-consuming, and has low availability as well as low sensitivity in the early stage (13,14). Thoracic CT is one of the first preferred imaging techniques due to its ease of accessibility and high sensitivity in the diagnosis of COVID-19 patients. In some studies, thoracic CT is found to have a sensitivity of 98% in the early stages of the diseases (7). The most common CT finding of COVID-19 pneumonia is ground-glass areas with a mostly bilateral and posterior localization, although unilateral involvement may sometimes be observed (14-16). Consolidation, which is less common, can be present either alone or in combination with a ground-glass area.

Serum ferritin and CRP levels increase in case of excessive inflammation due to infection. Although ferritin reflects normal serum iron levels, the levels of circulating ferritin increase during viral infections (17,18). It was reported in studies that C-reactive protein returns to normal earlier than ferritin in COVID-19 patients, and that the use of CRP in disease follow-up is therefore limited (17,19).

In our study, we examined the relationship between serum CRP and ferritin levels and thoracic CT parenchymal involvement in patients with a diagnosis that was

confirmed clinically and by PCR testing. Thoracic CT examination revealed no evidence of disease in the lung parenchyma in 92 (39.7%) patients, while parenchymal involvement was observed in 140 (60.3%) patients. With regard to the morphologic features of the parenchyma in patients with lung involvement, 74 patients had only ground-glass areas, 32 patients had only consolidation and 34 patients had both ground-glass areas and consolidation. In this study, the most common finding that was consistent with the literature was ground-glass areas (20-23).

It was reported in some studies that COVID-19 patients with high ferritin levels stayed longer in intensive care, that lung involvement was more severe and the mortality rate was higher in these patients (9,19,24,25). Therefore, identifying and treating these patients with a high mortality risk is important for survival. It was suggested in a study that the increase in ferritin serum levels is directly proportional to the severity of COVID-19 (11). Considering that lung involvement is one of the important complications of the disease, serum ferritin values were higher in the patient group with involvement than in the patient group without involvement and there was a statistically significant difference in our study. However, we found no significant difference between the patient groups with involvement at morphologically different periods. Furthermore, our study also demonstrates that ferritin may have diagnostic power with a sensitivity of 72.46% and specificity of 64.2% when the cut-off value of ferritin is considered to be 71.5 ml/ng to differentiate patients with positive CT findings.

It was reported in some studies that serum CRP values increase in the presence or increased severity of pulmonary involvement (9, 26,27). However, we found in our study that there was no statistically significant difference in CRP serum values between patients with and without CT findings. On the other hand, there was a significant and positive, albeit weak, relation between the ferritin and CRP serum according to the result of the Pearson correlation analysis.

CONCLUSION

Laboratory data are crucial in establishing the diagnosis, treatment, and prognosis in COVID-19 patients. Biomarkers such as serum CRP, ferritin, D-dimer, troponin, prothrombin time (PT) and IL-6 are most commonly used to identify these patients. In addition to these markers, radiologic imaging is required due to the primary lung involvement caused by the disease and CT is most commonly preferred thanks to its high sensitivity. In this study, we examined the relationship between serum CRP and ferritin levels and lung involvement in COVID-19 patients and established that there is a strong correlation between serum ferritin levels and lung involvement. Considering the radiation exposure caused by CT scans as well as the cost of the procedure, we are convinced that serum ferritin levels may help clinicians in terms of early diagnosis, especially in patients with suspected lung involvement. Nonetheless, more research is needed to say that there is a definite relationship. In addition, to the best of our knowledge, this is the first study to evaluate the diagnostic capability of ferritin in detecting COVID-19 pneumonia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Siirt University Non-invasive Ethics Committee (Date: 05.01.2023, Decision No: 64349).

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 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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Percutaneous steroid injection versus oral NSAIDs on treatment of symptomatic calcific rotator cuff tendinitis: a short-term retrospective clinical evaluation

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ABSTRACT

Aim: Symptomatic calcific rotator cuff tendinopathies (CRCT) continue to be a significant health problem in the adult population because of intense pain and disability. Different clinical responses obtained with different treatment modalities show us the importance of determining the optimal method. The aim of this study is to compare short term pain and functional status improvements in adult patients diagnosed with CRCT and treated with oral non-steroid anti-inflammatory drugs (O-NSAID) or percutaneous steroid injections (PSI).

Material and Method: A retrospective examination was made of the clinical results of adult patients diagnosed with CRCT and treated with one of the two treatment methods. Whole study group was formed of 40 patients (20 male, 20 female) with a mean age of 42.35 ± 8.28 (range, 23-57) years. The clinical responses of the patients in a period of 3 months were compared between the two treatment groups O-NSAID, PSI using the Visual Analogue Scale (VAS) and the Quick Disability of the Arm, Shoulder, and Hand Scale (Q-DASH). The angular upper limit values of the active range of motion (ROM) of the shoulder joint (anteflexion and abduction angle) of patients also were compared in the study.

Results: In the PSI treatment group, in the 3rd week and 3rd month clinical evaluations, significant better responses were obtained in both the VAS and Q-DASH scores of the patients compared to O-NSAID treatment group (p=0.000, p=0.001, respectively). And significant greater shoulder anteflexion and abduction ROM upper limits were determined in the PSI treament group compared to O-NSAID treatment group at the end of the 3rd month (p=0.000, p=0.000, respectively).

Conclusion: The percutaneous steroid applications in treatment of CRCT can provide more pleasing short term results than O-NSAID treatments in terms of pain reduction and functional improvement.

Keywords: Calcific tendinopathy, rotator cuff, injection, steroid

INTRODUCTION

Shoulder pain is frequently encountered in the community and is a frequent reason for referral to orthopedic clinics and physical therapy units. The one-year prevalence has been reported in the range of 4.7%-46.7% in various series (1). There can be many ethiologies for pain in the shoulder region, such as arthrosis, rotator cuff tendinopathy, subacromial impingement, bursitis, or suprascapular nerve entrapment (2-5). This condition has a serious social and psychological effect other than health problems on patients, and can be a cause of disability (6). Rotator cuff tendinopathies can develop as a result of subacromial impingement or for intrinsic reasons (7). Sometimes these tendinopathies accompany calcium deposits in the muscle-tendinous structure or subacromial-subdeltoid bursa and can become an intensely painful condition which is termed as calcific rotator cuff tendinopathy (CRCT) (4). The prevalence of CRCT has been reported at rates varying from 7% to 42% in various published studies (8,9).

CRCTs can be diagnosed on X-ray, ultrasound, or magnetic resonance imaging (MRI) (10). The etiology of CRCT has not been clarified as yet but the probable mechanism is thought to be due to metaplasia of tenocytes to calcium-producing chondrocytes (4,9). The natural progression of untreated CRCT may lead to adhesive capsulitis, cuff tear or ossifying tendinitis (11). Different treatment methods described to date include extracorporeal shock wave therapy (ESWT), kinesio banding, platelet-rich plasma (PRP) administration, physical therapy and arthroscopic interventions (4,8,10,12,13). Non-surgical methods from

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these treatments have been reported to have sufficient efficacy, and therefore it has been stated that these constitute the primary treatment methods (8). From these treatment methods, percutaneous treatment modalities are an effective and minimally invasive method (14-17). It has been reported that steroid treatment via percutaneous injections directed at painful calcium deposits reduces pain and provides sufficient resolution of mass effect of those deposits (15). The main aim of non-surgical methods is to provide improvement in the joint ROM, after the pain has subsided, with a physical therapy process. When no response is obtained to conservative treatments, and symptoms and findings persist, surgical options should be considered. Open or arthroscopic surgical methods aim to remove calcium deposits from the subacromial region and reduce mechanical irritation (18). The cost of interventional procedures in private hospitals, the fear of injections of patients and medical risks create hesitation in patients lead physicians towards non-invasive treatments among conservative solutions. Until now, no study has been published on the comparison of percutaneous steroid administrations and NSAID for patients with CRCT. The aim of this study was to retrospectively compare the functional gains and amount of pain reduction in patients diagnosed with CRCT and treated with O-NSAID or PSI (methyl-prednisolone + prilocaine combination) applications.

The study hypothesis is that the application of PSI in CRCT may provide better pain reduction and functional improvement compared to O-NSAID treatment methods, because of acute calcium deposit dissolvement.

MATERIAL AND METHOD

Ethics

The study was carried out with the permission of Memorial Ankara Hospital Ethics Committee (Date: 13.04.2023, Decision No:2023-2/1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participant

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A retrospective evaluation was made of the clinical and radiological data of 40 adult patients who were diagnosed with symptomatic CRCT and treated with one of treatment modalities (O-NSAID, PSI) between 2020 January and 2023 March, in orthopaedics clinic. These patients were separated into two groups as 21 patients treated with O-NSAID and 19 patients treated with PSI. The clinical responses of the patients were examined and compared with each other according to the treatment and based on time.

The CRCT diagnose criteria have been accepted in the investigated patients confirmed with observing painful calcium deposits in subacromial or subdeltoid locations on anteroposterior X-rays of shoulder. The study exclusion criteria of patients were defined as determining any acute or chronic infection, a history of smoking, known collagen tissue disease, or a diagnosis of diabetes mellitus.

In normal clinical practice, the application of PSI to all patients that have symptomatic CRCT is recommended in the light of current literature, but some of the patients do not accept the risks of the interventions.

In this study, the patients that did not accept the PSI applications and treated with oral NSAID formed the O-NSAID group. And the patients who underwent percutaneous steroid applications constituted the PSI group. For evaluation of clinic responses of the patient's visual analogue scale (VAS) and Quick-Dysability of the Arm, Shoulder and Hand Scale (Q-DASH) scores, and the shoulder upper limit values (anteflexion and abduction angle) have been investigated from the patients file records. And results were compared within each group and between the two treatment groups according to time (pre-treatment, 3rd week, 3rd month). All of those datas obtained from hospital file records after study protocol established, since study designed in retrospective manner.

Imaging

Conventional radiography: In the diagnosis of CRCT, calcium deposits can be seen on X-ray within the soft tissue in the subacromial region and subdeltoid regions (proximal humerus around the shoulder). The localisation and morphology of calcium deposits can be understood on standard anteroposterior (AP), outlet, and axillary view images. The radiological classification of CRCT on X-ray was defined by Mole et al. (19). This classification is made according to calcium deposits as Type A: sharply defined, homogenous and dense calcification, Type B: sharply defined, dense in appearance, with multiple fragments, Type C: heterogeneous calcification in appearance, with a downy deposit, and Type D: dystrophic calcification in the tendon insertion. Gosen et al. (10) reported that Type C and Type D may show the resorptive phase. Gärtner and Heyer (20) separated CRCT into 3 types radiologically subtypes. In Type I calcium deposits are evident in the surroundings and there are lesions with intense calcifications (formation phase). In Type II, there are lesions with soft contours containing less intense calcification, and in Type III there are translucent lesions showing cloudy calcification (resorptive phase). In the study patients PSI treatments were applied by confirming calcified soft tissue areas on the X-rays that were sensitive on clinical examination.

During the application calcium deposits dissolvement was confirmed with fluoroscopic imaging (Figure 1). After the applications dissolvement has been also confirmed on X-ray (Figure 2). All the conventional imaging methods used for these patients were for usual clinical application, in treatment way. And all of those X-ray images were obtained from the radiology department after current study protocol designed. All the patients examined in current study were diagnosed with the AP X-ray and all patients diagnosed as CRCT were classified as Type B which defined by Mole et al. (19). In the study patients PSI treatments were applied by confirming calcified soft tissue areas on the X-rays that were sensitive on clinical examination. During the application calcium deposits dissolvement was confirmed with fluoroscopic imaging (**Figure 1**). After the applications dissolvement has been also confirmed on X-ray (**Figure 2**). All the conventional imaging methods used for these patients were for usual clinical application, in treatment way. And all of those X-ray images were obtained from the radiology department after current study protocol designed.

Magnetic resonance imaging: MRI is important in the musculoskeletal imaging of the shoulder region. However, protons with low resonance within the calcium deposits lead to low resolution of calcification deposits (21). If calcium deposits are oedematous, they can mimic tendon tear by causing signal changes. All the patients underwent MRI at the end of the 3rd month of treatment to determine potential tendon damage of those calcific deposits, for a routine control purpose in clinical practice. As the current study was designed retrospectively, MRI images were obtained from the radiology department after the study protocol was established. And no tendon rupture was detected in those images.

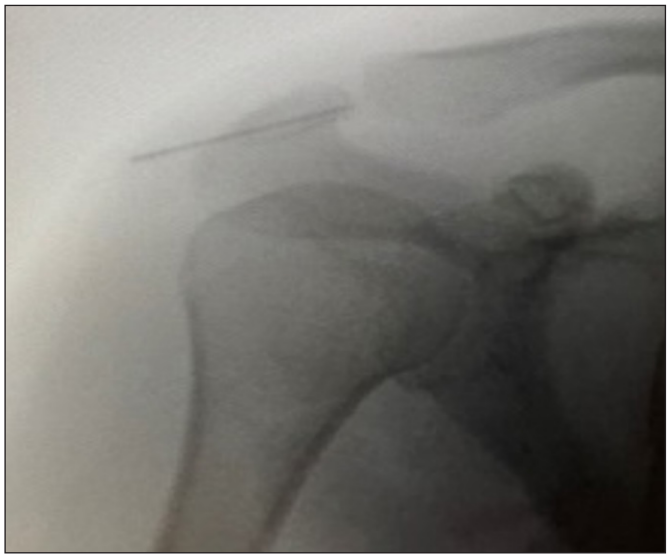

Figure 1. Flouroscopic view of dissolved calcium deposit region in a right shoulder of a patient diagnosed with CRCT, after PSI application.

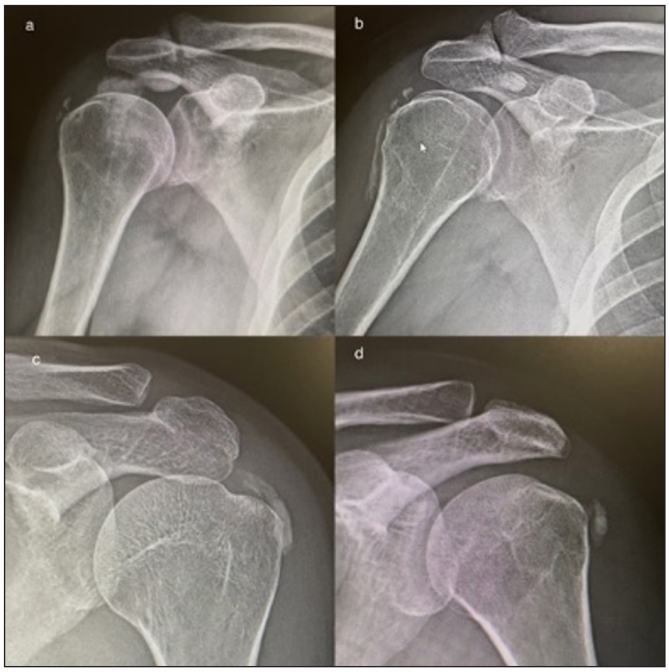

Figure 2. a.) Pre-treatment AP shoulder X-ray of a 47-year-old female patient with calcific deposits in the right shoulder subacromial region, b.) AP shoulder X-ray taken immediately after PSI of the same patient. c.) Pre-treatment AP X-ray of a 35-year-old female patient with calcific deposits in the left shoulder subdeltoid region, d.) AP X-ray of the same patient taken immediately after PSI.

Treatment Methods

Percutaneous steroid injection application: Calcific enthesopathies are basically painless and asymptomatic pathologies. When these ensethopathies are painful, the clinician can perform minimally invasive interventions targeting these lesions. The most frequently applied of these minimally invasive interventions is percutaneous injection method. Dry needling also is a different minimally invasive method that has been described for painful lesions. The ability to dissolve calcium deposits is important in respect of the regression of impingement findings and being able to prevent potential rotator cuff damage. Therefore, steroid injections targeting to volume occupying calcium deposits and/or drainage of those deposits with percutaneous fluids seem to be rational (4). Applications with a single or double needle can be made (17). To date, different fluid types (steroid types, lidocaine, hyaluronic acid, PRP) have been reported that applied through the injection route (17). In the current study, the PSI group was formed of patients diagnosed with CRCT who were applied with the combination of 1ml 40 mg methyl-prednisolone + 2 ml 2% prilocaine + 2 ml sterile sodium chloride solution to painful calcific lesions in the subacromial and/or subdeltoid regions (**Figure 1**). And all the injections have been applicate by a single senior orthopaedist, in a same manner for every patient.

Oral NSAID treatment: In the current study the patients that have been found in O-NSAID treatment group had been used Naproxen Sodium 750 mg per day for pain relief and improvement of functional status. All the patients in O-NSAID treatment group has been taken 2 box of pills because of intense pain, this means 3-week usage for treatment.

Physical treatment and rehabilitation: All the patients, that have belonged to two different treatment groups, has started physiotherapy programs in same clinic at 3rd week after start of treatment, for a six-week program. Those therapy programs have been including muscle stretches and ROM exercises.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS (22.0 version software SPSS Inc., Chicago, IL, USA). Descriptive statistics were stated as mean ± standard deviation (SD) values for continuous variables with normal distribution, as median (range) values for variables not showing normal distribution, and as number (n) and percentage (%) for categorical variables. Suitability of the data to normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. With the exception of age, all the other variables did not show normal distribution. In the comparisons of the median values of two independent groups, the Mann Whitney U-test was used, and for more than two groups, Kruskal Wallis variance analysis was applied. To determine from which group the difference originated after variance analysis, post-hoc paired comparison tests were used. A value of p <0.05 was accepted as statistically significant.

RESULTS

The data were analyzed of a total of 40 patients. The O-NSAID group of 21 (52.5%) patients comprised 11 females and 10 males with a mean age of 41.19 ± 7.12 (range, 22-51) years. The PSI group of 19 (47.5%) patients comprised 9 females and 10 males with a mean age of 43.42 ± 9.46 (range, 27-57) years. The dominant side was right-side in 25 (62.5%) patients and left-side in 15 (37.5%). No significant difference was determined between the groups in respect of age, gender, and dominant side (p>0.05). The time to diagnosis was median 2 (1-3) days in the O-NSAID group, and median 2 (1-2) days in the PSI group, with no statistically significant difference determined (p>0.05) (**Table 1**).

In both of O-NSAID and PSI groups according to the results of the Kruskal Wallis test, significant differences were determined between the VAS scores pre-treatment, on the 3rd post-treatment weeks, and at the end of the 3rd months (p<0.05). And according to the results of the Mann Whitney U test, the median VAS scores of both groups showed a statistically significant difference between the 3rd week and the 3rd month (p<0.05) (**Table 2**).

Table 1. Baseline characteristics in patients in the whole study group with CRCT

	O-NSAID group n=21	PSI group n=19	P value
Gender (F/M)	11/10	9/10	.752[a]
Dominant side	13/8	12/7	.935[a]
	m±sd (range)	**m±sd (range)**	
Age	41.19 ± 7.12 (23-51)	43.42 ± 9.46 (27-57)	.402[b]
	median (range)	**median (range)**	
Time to diagnosis (days)	2 (1-3)	2 (1-2)	.520[c]

a Pearson Chi-Square test with frequencies, b Student T test with mean ± SD values, c Mann Whitney U Test with median (range) values, M: mean, SD: standard deviation, O-NSAID: Oral Non-Steroid Anti-Inflammatory Drug, PSI: Percutaneous Steroid Injections

Table 2. The clinical results of the different treatment methods according to the VAS scores of the groups

		VAS Score				
	n	Pre-treatment (1)	3rd week (2)	3rd month (3)	P value	Post Hoc P value
O-NSAID group	21	8 (7-9)	7 (6-8)	6 (5-7)	.000[b*]	1-2: .011* 1-3: .000* 2-3: .000*
PSI group	19	8 (7-9)	4 (3-5)	2 (1-4)	.000[b]	1-2: .001* 1-3: .000* 2-3: .003*
P value		.940[a]	.000[a]	.001[a]		

a Mann Whitney U Test with median (range) values, b Kruskal Wallis Test with median (range) values, O-NSAID: Oral Non-Steroid Anti-Inflammatory Drug, PSI: Percutaneous Steroid Injections

In both of O-NSAID and PSI groups according to the results of the Mann Whitney U test, significant differences were determined between the Quick-DASH scores pre-treatment, on the 3rd post-treatment weeks, and at the end of the 3rd months (p<0.05). And according to the results of the Kruskal Wallis test, the median Quick-DASH scores of both groups showed a statistically significant difference between the 3rd week and the 3rd month (p<0.05) (**Table 3**).

Table 3. The clinical results of the different treatment methods according to the Quick-DASH scores of the groups

		Quick-DASH score				
	n	Pre-treatment (1)	3rd week (2)	3rd month (3)	P value	Post Hoc P value
O-NSAID group	21	92.5 (90-97.5)	85 (82.5-90)	50 (45-60)	.000[b*]	1-2: .001* 1-3: .000* 2-3: .001*
PSI group	19	92.5 (87.5-97.5)	62.5 (57.5-65)	17.5 (12.5-20)	.000[b*]	1-2: .001* 1-3: .000* 2-3: .001*
P value		.748 a	.000 a*	.000 a*		

a Mann Whitney U Test with median (range) values, b Kruskal Wallis Test with median (range) values, O-NSAID: Oral Non-Steroid Anti-Inflammatory Drug, PSI: Percutaneous Steroid Injections

No difference was determined between the O-NSAID group and the PSI group in respect of the pre-treatment median values of the shoulder anteflexion and abduction angle upper limits. A significant difference was determined in all groups by mean of anteflexion and abduction in respect of values at the end of 3rd months ($p<0.05$). A significant difference was determined between the groups in respect of the values at the end of 3rd months by mean of anteflexion and abduction angle upper limits ($p<0.05$) (**Table 4**). The gains in terms of both pain reduction and functional improvement has been presented as VAS and Quick-DASH Score boxplot diagrams in **Figure 3** and **4**.

Table 4. The change in upper limits of active shoulder ROM in patients according to time in different treatment type groups

ROM		O-NSAID group n=21	PSI group n=19	P value
Shoulder anteflexion upper limit (°)	Pre-treatment	20 (10-30)	20 (15-30)	.258
	3rd month	45 (30-55)	90 (75-90)	.000*
	P value	.000*	.000*	
Shoulder abduction upper limit (°)	Pre-treatment	20 (10-25)	20 (10-25)	.270
	3rd month	45 (40-55)	80 (70-90)	.000*
	P value	.000*	.000*	

Mann Whitney U Test with median (range) values, * $p<0.05$, ROM: Range of Motion, O-NSAID: Oral Non-Steroid Anti-Inflammatory Drug, PSI: Percutaneous Steroid Injections, °:Degree

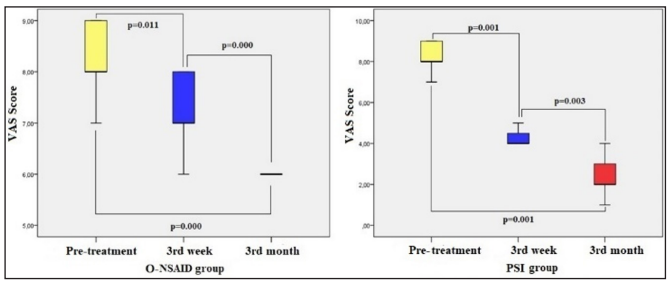

Figure 3. Boxplot showing the distribution of VAS score measurements pre-treatment treatment, on the 3rd week of treatment and at the end of the 3rd month of treatment

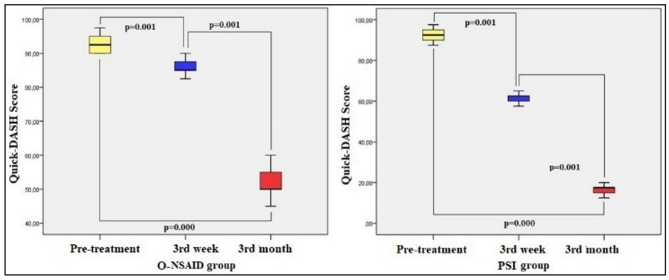

Figure 4. Boxplot showing the distribution of Quick-DASH scores pre-treatment, on the 3rd week of treatment and at the end of the 3rd month of treatment

DISCUSSION

It has been reported that CRCT diagnosis can be made with US or conventional radiologic techniques in patients with acute and intense painful shoulder condition (4). And mostly those calcium deposits may continue with ongoing clinical findings such as pain and disability in those patients without treatment (22). Percutaneous applications in the treatment of CRCT aim to dissolve painful calcium deposits. For this purpose, different fluids (including PRP, stem cells, sodium chloride, steroid, prolotherapy) have been presented in different papers for many times (16,23,24).

Imaging-guided minimally invasive injections have been reported to obtain effective results in CRCTs at rates of up to 80% (8). Greis et al. (8) also stated that sufficient responses could be obtained with non-surgical methods in the majority of cases. And Simpson et al. (25) showed that percutanous interventions were more effective in terms of pain reduction and functional improvement than ESWT applications. In current study the obtained data showed that lower VAS and Q-DASH scores were obtained in PSI applicated patients, compared to patients which treated with O-NSAID (**Table 2,3**). Moreover, a significant increase in shoulder joint ROM was determined in patients after PSI application compared to patients that treated with O-NSAID (**Table 4**).

In a study by Louwerens et al. (26), similar successful function and pain improvements were reported to have been obtained in a 1-year follow-up period after ultrasound-guided needling combined with a subacromial steroid injection and ESWT. But calcium deposits were seen to have benefitted more from the steroid injections by mean of dissolvement in same study (26). Dumoulin et al. (27) reported that treatments to be applied providing subacromial bursa communication with the calcium deposits in CRCT patients would be effective in the radiological and clinical results. In current study all the patient's calcium deposits have been dissolved with the PSI application successfully and this condition has been confirmed with fluoroscopic imaging. And the PSI applications in the current study in patients, were applied in way so that in patients with multiloculated calcium deposits, communication between lesions would be provided in the subacromial and subdeltoid bursa regions by injection application trajectory. In the light of the data obtained, it was thought that good pain improvement and functional gain, could be related to the PSI application targeting all the calcified foci.

Although the percutaneous application of these fluids has an important place in CRCT treatment in respect of pain and functional improvements, it may cause complications such as septic bursitis and vasovagal syncope (4). In the current study, we didn't determine any complications related to PSI application in any patient.

Azevedo et al. (28) reported that early interventions to painful calcific lesions in the shoulder region had most important prognostic factor on treatment response.

In the current study, the treatment process for all the patients was determined to have been started within three days after the onset of the clinical complaints. The positive clinical responses obtained in the two different treatment methods suggest that success also could be closely related with timing in treatment initiation other than treatment modality.

Limitations

First of all, the patient groups did not show normal distribution so the statistical analyses were performed with non-parametric tests. More significant interpretations may be able to be made in further studies of larger patient series so that normal distribution can be obtained and analyses can be made with parametric tests. Secondly, long-term results of the patients were not evaluated clinically or radiologically as the patients did not attend follow-up appointments, which was thought to be because the complaints had greatly decreased. Therefore, further studies to obtain data from longer term follow-up would be able to provide more detailed information about the long-term clinical results.

CONCLUSION

In the treatment of symptomatic calcific rotator cuff tendinitis, better pain and functional results can be obtained with the percutaneous steroid injections compared to oral NSAIDS, in short term. In those minimal invasive applications targeting all of the calcific lesions and doing that at the early time of diagnosis, it would be correct to think that the treatment success is increased.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Memorial Ankara Hospital Ethics Committee (Date: 13.04.2023, Decision No:2023-2/1).

Informed Consent: Because the study was designed retrospectively, no written informed consent needed.

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 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 effect of granulocyte transfusion on engraftment in patients with allogeneic hematopoietic stem cell transplantation

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ABSTRACT

Aim: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is still one of the most effective treatments for many hematological malignancies. However, especially infections and neutropenic fever increase mortality during the engraftment development process after allo-HSCT. This study investigated the effect and safety profile of granulocyte transfusion (GT) on engraftment in patients with neutropenic fever after allo-HSCT.

Material and Method: We investigated 32 patients with hematological malignancies who had neutropenic fever following allo-HSCT between June 2018 and February 2020. Seventeen patients were given GT and defined as GT group (GTG). GT was given once daily until improvement in clinical and laboratory parameters (neutrophil >0.5 $\times10^3$/μL, platelet >20 $\times10^3$/μL). Fifteen patients who did not receive GT were included as a control group (CG).

Results: By comparing leukocyte levels between the start and end of GT, the median leukocyte increase was shown as 1.93 (0.37- 10.21) $\times10^3$/μL (p=0.001). Similarly, the median neutrophil increase was 1.14 (0.25-9.24) $\times10^3$/μL (p=0.001). A total of 65 GTs were administered, the average number of days was 4±1. The average dose of infused granulocyte was 4 $\times10^{10}$/unit. In GTG, neutrophil and platelet engraftments occurred on average at 14±2 and 10±2 days, respectively. In CG, neutrophil and platelet engraftments occurred on average 15±2 and 12±3 days, respectively. There was no statistically significant difference in neutrophil and platelet engraftment between the two groups (p=0.4, p=0.06, respectively).

Conclusion: GT was observed to be effective in managing complications such as neutropenic fever and sepsis after allo-HSCT by shortening the duration of neutropenia and increasing neutrophil and leukocyte values. Although statistical significance was not observed in our study, it was observed that the engraftment times were shortened with GT.

Keywords: Allogeneic transplantation, engraftment, granulocyte transfusion

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for many hematological malignancies. However, the success of allo-HSCT is often limited by delayed engraftment, which can lead to a higher risk of infection with severe morbidity and mortality (1). It is necessary for successful treatment in these patients to recover from neutropenia and use an appropriate and effective antimicrobial agent(s). Although broad-spectrum antibiotics and antifungal treatments have been introduced, infection remains a major cause of death in patients with allo-HSCT.

Granulocyte transfusion (GT) is a sensible therapeutic approach as a replacement therapy if infection control cannot be achieved despite these treatments (2). The survival effect of GT therapy in the presence of severe sepsis and invasive fungal infection in patients with an intrinsic defect in neutrophil function or neutropenia has been discussed in various studies and reported to be effective in most (1, 2).

It has been shown that GT administration against infections in neutropenic patients after allo-HSCT reduces infection-related morbidity and mortality (3). However, the effect of GT on engraftment in these patients was not evaluated. Therefore, we aimed to evaluate the effect of GT on hematological and clinical response in patients undergoing allo-HSCT, with a particular focus on its contribution to neutrophil and thrombocyte engraftment.

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MATERIAL AND METHODS

The study was carried out with the permission of Erciyes University Faculty of Medicine Ethics Committee (Date: 12.02.2020, Decision No:2020/126). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Thirty-two patients with neutropenic fever after allo-HSCT were included in this retrospective study between June 2018 and February 2020 at the Department of Bone Marrow Transplantation at Erciyes University. Seventeen patients were given GT and defined as GT group (GTG). GT was given once daily until improvement in clinical and laboratory parameters (neutrophil >0.5 $\times10^3$/μL, platelet >20 $\times10^3$/μL). Fifteen patients who did not receive GT were included as a control group (CG). Patients in both groups were treated with necessary antibiotics, antivirals, and antifungals.

Patients under the age of 18 and over 65 were not included in the study. Age, gender, weight, height, and diagnoses of patients were recorded. The granulocyte donor was selected according to the criteria for being a standard blood donor from non-related relatives or voluntary healthy donors. All donors before transfusion, immuno-hematological acceptance tests (blood group and crossmatch), compatible and infection screening tests (HIV, hepatitis B, hepatitis C, CMV, syphilis serology), seronegative and complete blood count were in good health. The Spectra Optia device was used for granulocyte collection.

Donors were stimulated to collect granulocytes with granulocyte colony-stimulating factor (G-CSF) and oral 8 mg dexamethasone 12 hours before apheresis. No donor had any side effects that required the collection to be stopped. The granulocyte was irradiated with 25 Gy before being infused. The objective cell dose given to the patient by granulocyte infusion was at least 1×10^{10} per transfusion. In patients taking amphotericin B for fungal infection, it was noted that there was a minimum of six hours between GT and amphotericin B administration. Transfusion was usually performed between 30-45 minutes. No severe side effects were observed in the patient when applying granulocytes. GT was continued daily and as long as the donor could be provided until the absolute neutrophil number rose above 0.5×10^9/L or until clinically signs of infection were controlled. Patients who received granulocytes for consecutive days were included in our study. Granulocyte was given for at least three days, and no more than six days.

Allo-HSCT was performed to 101 patients in our center between June 2018 and February 2020. GT was given to 17 (17%) of them. GT administration is considered in all allo-HSCT patients when an adequate response is not achieved with antibiotic therapy in our center. However, GT cannot be given when an unrelated or voluntary donor suitable for GT cannot be found or if the donor found is not suitable as a result of the tests. In our study, GT was given to 17 of 32 patients, but GT could not be given to 15 (47%) of the aforementioned reasons, and they were taken as the control group.

Engraftment has at least three consecutive days of absolute neutrophil count >500/mm³ and platelet count >20×10^3/μL (3). Leukocyte, platelet, and neutrophil values were noted every day until engraftment occurred. Granulocyte infusion dose, granulocyte day count, engraftment day, clinical response, hematological response, and mortality status were followed. Clinical response to granulocyte transfusion was defined as a clinical benefit of the patient, a decrease in fever, control of infection, and the inability to show reproduction in the culture previously in the control culture.

Statistical Analysis

In our study, the SPSS 22 (IBM) package program was used to evaluate the data analysis. Descriptive statistics (the Kolmogorov-Smirnov/ Shapiro-Wilk tests) and graphs (histogram and probability) were used to create Central and prevalence criteria such as percentage, number, minimum, maximum, mean, standard deviation. In descriptive analyses, mean and standard deviation (mean±standard deviation) were used for normally distributed variables, while median and minimum-maximum values (median± min-max) were used for normal non-distributed variables. The Mann-Whitney U test was used for independent variables compared to 2 variables that were found not to match the normal distribution. The Wilcoxon test was used to compare two dependent variables that do not match the Normal distribution. The Chi-square test was used to determine the difference between categorical variables. The correlation between numerical data was evaluated by Spearman correlation analysis, as the variables did not correspond to the normal distribution. Overall survival (OS) was measured as the time from allo-HSCT to death regardless of any cause. Results were considered in the 95% confidence range, statistical flood significance $p<0.05$.

RESULTS

The main characteristics of the 32 patients who had neutropenic fever after allo-HSCT are presented in **Table 1**. Seventeen (53.1%) patients were given GT and defined as GT group (GTG). The other 15 (46.9%) patients did not receive GT and were named the control group (CG). Of these, 16 (50%) were female, and 16 (50%) were male. The median age in the GTG and CG was 44 (29-62) and 50 (26-65) years, respectively (p=0.14).

Table 1. Main characteristics of the study population

	Granulocyte group (n:17)	Control group (n:15)	P
Age, years, median (range)	44 (29-62)	50 (26-65)	0.143
Gender, n (%)			0.3
Female	10 (59%)	6 (40%)	
Male	7 (41%)	9 (60%)	
Disease, n (%)			1.0
Acute myeloid leukemia	9 (53%)	11 (73%)	
Acute lymphoid leukemia	3 (17%)	2 (13%)	
Hodgkin lymphoma	2 (12%)	-	
Aplastic anemia	2 (12%)	-	
Myelodysplastic syndrome	1 (5%)	1 (7%)	
Diffuse large B-cell lymphoma	-	1 (7%)	
Neutrophil engraftment (day)±standard deviation	14±2	15±2	0.403
Platelet engraftment (day)±standard deviation	10±2	12±3	0.058
Underlying infections, n (%)			
Bacterial	12 (70.5%)	11 (73%)	0.86
Fungal	8 (47%)	8 (53%)	0.72
Viral	5 (29%)	3 (20%)	0.54
Pneumonia	7 (41%)	8 (53%)	0.49
CMV viremia	5 (29%)	2 (13%)	0.27
Aspergillosis	2	1 (7%)	0.62
Mucositis	7 (41%)	8 (53%)	0.49
Colitis	4	2 (13%)	0.46
Donor, n (%)			0.26
Matched related	8 (47%)	10 (67%)	
Haploidentical related	9 (53%)	5 (33%)	
Stem cell source, n (%)			0.62
Peripheral blood	15 (88%)	14 (93%)	
Bone marrow	2 (12%)	1 (7%)	
Conditioning regimen, n (%)			0.89
Myeloablative	15 (88%)	13 (87%)	
Reduced intensity	2 (12%)	2 (13%)	
Antithymocyte globulin	7 (41%)	5 (33%)	0.65

Haploidentical allo-HSCT was higher in GTG (53% (n=9) versus 33% (n=5)), but no statistically significant difference was observed in terms of all allo-HSCT features and underlying infection types (p>0.05 in all) (**Table 1**). Except for grade 2 allergic reaction in 2 (12%) patients, no other side effects related to GT were observed. On the 20th day, leukocyte values in the CG and GTG were 0.9 (0.75-1.33) $\times 10^3/\mu L$ and 2.17 (0.31-6.24) $\times 10^3/\mu L$, respectively (p=0.9), and neutrophil values were 0.85 (0.26-2.14) $\times 10^3/\mu L$ and 1.93 (1.45-2.95) $\times 10^3/\mu L$, respectively (p=0.71). Leukocyte and neutrophil values after allo-HSCT were showed in **Figures 1** and **2**.

The average neutrophil and platelet engraftment was observed on the 15th and 11th day, respectively. A total of 65 GTs were performed, and the average number of days was 4 ±1. The infused granulocyte dose averaged $4x10^{10}$/unit. The time to start the GT was in the median of 11 (5-17) days. There was no statistically significant difference in leukocyte, neutrophil, platelet values on transplant day between the granulocyte and control groups (p=0.49, p=0.36, p=0.16, respectively).

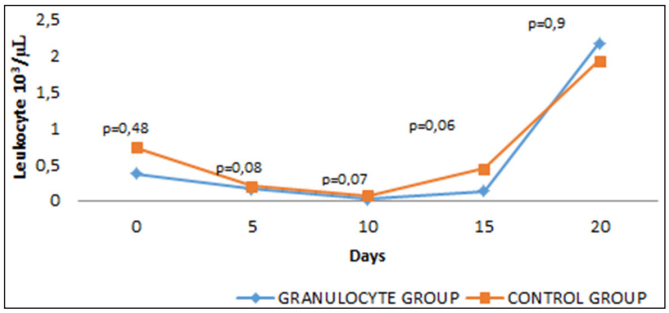

Figure 1. Distribution of leukocyte values of granulocyte and control groups according to day.

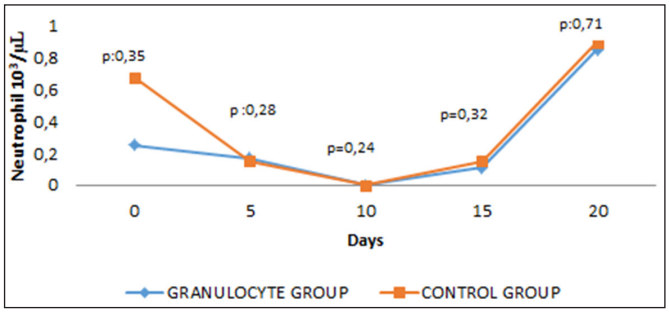

Figure 2. Distribution of neutrophil values of granulocyte and control groups according to day.

A median increase in leukocytes was 1.93 (0.37-10.21) $\times 10^3/\mu L$ compared to the beginning and end of GT. A statistically significant difference was found between GT and leukocyte increase (p=0.001). Similarly, the median neutrophil increase was 1.14 (0.25-9.24) $\times 10^3/\mu L$. A statistically significant difference was found between GT and neutrophil increase (p=0.001). In GTG, neutrophil and platelet engraftments occurred on average at 14±2 and 10±2 days, respectively. In CG, neutrophil and platelet engraftments occurred on average 15±2 and 12±3 days, respectively. There was no statistically significant difference in neutrophil and platelet engraftment between the two groups (p=0.4, p=0.06, respectively).

Clinical response after GT was evaluated. Eight (47%) of 17 patients had a clinical response, but 9 (53%) patients did not have. The hematological response was achieved in 15 (88%) of 17 patients. Clinical response was obtained in all 8 (53%) patients who received a hematological response. Only hematological response was observed in 6 (40%) patients without a clinical response (p=0.2).

The median follow-up time was 9 (1-48) months. The mean OS was 34.3±4.9 (24.5-44.1) months in CG and 18.4±4.9 (8.7-28.1) months in GTG (p=0.035) (**Figure 3**). Five (29%) patients died in the first month after GT, and 7 (41%) died in the first three months. In the

CG, four (26%) died in the first three months. More deaths in the GTG arm were thought to be due to having more haploidentical allo-HSCT than the CG arm. There was no statistically significant difference between neutrophil and platelet engraftment time and mortality (**Table 2**). Relapse was observed in 2 (11.8%) patients in GTG and not in any patient in CG. While infection-related mortality developed in 2 (11.8%) patients in GTG, it developed in 3 (20%) patients in CG. Graft versus host disease-related mortality was observed in 17.6% (n=3) of the patients in GTG, and in 1 (6.7%) of the patients in CG.

Table 2. Effect of neutrophil and platelet engraftment durations on mortality

		Neutrophil Engraftment Day			Platelet Engraftment Day		
		≤15	>15	p	≤11	>11	p
Granulocyte Group	Non-survivors	7	3	0.45	9	4	0.67
	Survivors	2	2		3	1	
Control Group	Non-survivors	1	3	0.46	1	3	0.34
	Survivors	5	6		6	5	

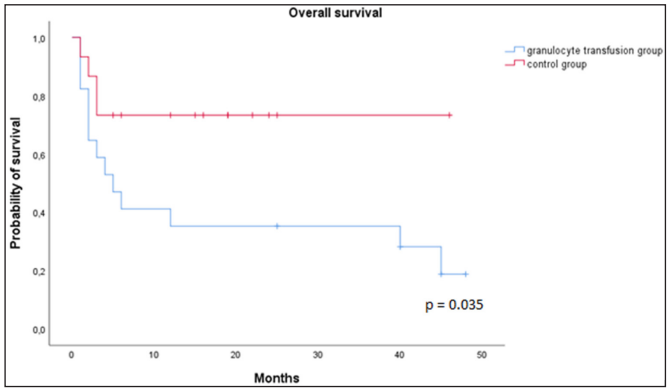

Figure 3. The cumulative survival chart of control and granulocyte group.

Sepsis was present in 7 (41.1%) patients in GTG, and in 6 (40%) patients in CG. In GTG, 23.5%(n=4) of the patients needed intensive care unit (ICU), 11.8%(n=2) needed mechanical ventilator (MV), 17.6%(n=3) needed vasopressors. In CG, ICU need developed in 5 (33.3%) patients, MV need developed in 4 (26.7%) patients, and vasopressor need developed in 5 (33.3%) patients.

DISCUSSION

Modern intensive chemotherapy for patients undergoing stem cell transplants often results in prolonged neutropenia periods, which is a significant risk factor for severe bacterial and fungal infections. In patients with febrile neutropenia, infection is the leading cause of morbidity and mortality, despite broad-spectrum antibacterial and antifungal agents and the necessary support treatments. The occurrence of multidrug-resistant bacterial and invasive fungal infections with the change in the spectrum of infections has led to problems in immunosuppressive patients over the past two decades. GT is a life-saving treatment method by increasing the number of peripheral granulocytes and reducing infection risk (5).

In CG patients, neutrophil and platelet engraftment occurred at average at 15 and 12 days, respectively; and in the GTG, neutrophil and platelet engraftment occurred at 14 and 10 days, respectively. Although there was no statistically significant difference, probably due to small population of the study, engraftment occurred faster in GTG.

The clinical response was defined as the return of fever to normal after transfusion and the clinical recovery. The hematological response was defined as improved laboratory parameters and was achieved in 15 (88%) of 17 patients. Differences in infection severity or infection factor may have caused this condition in patients where the clinical response was not achieved, although there was a hematological response. In a retrospective study conducted in 2016, a total of 25 patients were given GT, and the hematological response was observed in 21 (84%) of the patients, and no hematological response was observed in 4 (16%) (6). After GT in studies, hematological response and recovery rate of clinical symptoms were observed as 68,2%, 50%, and 40% respectively (7-9). In these studies, the occurrence of a lower hematological response may be due to the use of relatives as donors or the inclusion of patients with both allogeneic and autologous hematopoietic stem cell transplants.

In our study, neutrophils increased by 1.14 (0.25-9.24) $\times 10^3/\mu L$ after GT. This increase is higher than reported in other studies, showing a 0.6-2.6 $\times 10^3/\mu L$ neutrophil increase (10, 11). In another study, 84% of patients reported an increase in the number of neutrophils to 1 $\times 10^3/\mu L$ (6). The reason for the increase in neutrophil value at various levels in studies may be that patient groups' characteristics are different and affected by treatment methods other than GT.

Ikegawa et al. (12) administered GT 40 times in 13 patients after allo-HSCT and showed a one-month survival of 84.6% after GT. In the Resolving Infections in Neutropenia with Granulocytes (RING) study, adult and pediatric patients planned a collection of at least 4 $x10^{10}$ granulocytes per transfusion at a high target transfusion dose (13). For this purpose, before collecting, donors were given 480 µg G-CSF and 8 mg dexamethasone. Study groups were formed as high-dose granulocyte-receiving, low-dose granulocyte-

receiving, and a control group that did not receive granulocytes. At the end of 42 days, survival in the high-dose group was better than in the low-dose group (59% vs. 15%, p=0.01), while the control group was no better than in the high-dose group (59% vs. 37%, p=0.11) (13). In our study, 1-month survival with granulocyte administration was 70.5%.

In the study of Lee et al. (15) 54 patients had a pre-granulocyte leukocyte value of 0.18 (0.01-6.85) $\times 10^3/\mu L$, post-granulocyte leukocyte value increased to 0.96 (0.02-14,36) $\times 10^3/\mu L$ ($p<0.0001$) (14). In our study, the leukocyte value was 0.04 (0-0.25) $\times 10^3/\mu L$, 1.96 (0.61-10.4) $\times 10^3/\mu L$, respectively, and the increase was greater. The leukocyte response may have been different due to the use of dexamethasone only in the donors. In another retrospective study, GT obtained using dexamethasone combined with G-CSF was found to be more efficient than that obtained using G-CSF alone (16).

Ang et al. (17) showed that neither granulocyte dose nor neutrophil increase was associated with improved infection control or decreased mortality. In our study, a statistically significant difference was found between GT and neutrophil increase (p=0.001). This may be because the granulocyte collection from each donor was different once in the study. The dose of C-GSF used with dexamethasone in donor preparation was different, and the infused granulocyte dose and the pathogens causing the infection were different.

There were some limitations in our study, such as the number of patients, single center experience, and retrospective nature. Besides, unlike other studies, although it is advantageous to select only patients with allo-HSCT in terms of homogeneous distribution, all patients' primary diagnosis was not the same.

CONCLUSION

GT was observed to effectively manage complications such as neutropenic fever and sepsis after allo-HSCT by shortening the duration of neutropenia and increasing neutrophil and leukocyte values. Prospective, multi-center, further studies involving more homogeneous patient groups are needed to investigate the effects of GT on engraftment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Faculty of Medicine Ethics Committee (Date: 12.02.2020, Decision No:2020/126).

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 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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Sentinel lypmh node biopsy in early breast cancer: preliminary results of the combined technique of CT lymphography and blue-dye

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ABSTRACT

Aim: The aim of this study was to evaluate the efficacy of CT lymphography in sentinel lymph node biopsy for early stage breast cancer and to investigate its contribution to the conventional blue-dye method.

Material and Method: A total of 47 patients with early stage breast cancer underwent preoperative CT lymphography for lymph node mapping before sentinel lymph node biopsy with blue-dye method. The lymph nodes identified by CT lymphography and/or blue-dye method were examined for metastatic involvement. The sentinel lymph node detection rates of CT lymphography and blue-dye method were compared using t-tests.

Results: The sentinel lymph node detection rate with blue-dye method (87.2%) was significantly higher than with CT lymphography (66.0%) (P=0.027). However, the combined method (blue-dye method and/or CT lymphography) increased the detection rate (95.7%) (P=0.267). Benign sentinel lymph nodes were detected more often with CT lymphography (P=0.366), while metastatic sentinel lymph nodes were detected more often with blue-dye method (P=1,000). Upper outer quadrant tumors were detected less successfully with CT lymphography and more successfully with blue-dye method (P=0.220 and P=0.674, respectively). The success rate of CT lymphography in younger patients (less than 50 years old) was higher compared to older patients (P=0.001).

Conclusion: CT lymphography was found to be insufficient as a standalone method for sentinel lymph node biopsy. However, it could be used as a complementary method to blue-dye method to increase the success of sentinel lymph node detection.

Keywords: Breast cancer, CT lymphography, lymph nodes, sentinel lymph node, sentinel lymph node biopsy

INTRODUCTION

Axillary metastatic lymph nodes (LNs) can be detected using ultrasound (US) and magnetic resonance (MR) imaging (1-4). However, a negative result on US or MR does not exclude axillary node metastases due to their low negative predictive values. The accuracy of US, which also depends on the size and number of LNs, has been reported to range between 68% and 80% (4). In a meta-analysis of 23 studies, Zhou et al. (5) reported a pooled sensitivity of 77% and a pooled specificity of 90% for MR in detecting metastatic axillary LNs. Similarly, recent studies using FDG (6,7,8) and SPECT CT (9,10) to detect metastatic axillary LNs were promising but not accurate enough. Therefore, surgical staging of the clinical and radiologic node-negative axilla is still necessary in the treatment of early breast cancer.

Axillary LN dissection (ALND) is highly effective in staging and controlling local disease in breast cancer. However, due to the high risk of neurovascular and lymphatic complications and high morbidity, it has been replaced by sentinel LN biopsy (SLNB), which is a less invasive and highly accurate technique. A negative SLNB enables avoiding unnecessary ALND in patients with no metastatic axillary LNs (11-14). In cases where sentinel lymph nodes (SLN) cannot be detected and sampled, ALND has to be done.

Besides relatively new techniques such as MR (11,15) and US lymphography (16,17), SLNB is mostly performed using blue-dye (BD) and radioisotope lymphography (RIL) methods. The combination of BD and RIL methods for determining the SLNs is more effective than either

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method applied alone (18,19). However, RIL is not widely used in our country, mostly due to a lack of equipment. Therefore, in most centers, including our institution, SLNB is performed only with BD in daily routine practice.

In the early 2000s, SLN localization with CT lymphography (CTL) was introduced and widely used by Japanese physicians with highly accurate results (14,20-24). However, it is not a widely practiced method in Europe and the USA. In this paper, the authors present their preliminary results of a combined technique with BD and CTL methods for SLN localization.

MATERIAL AND METHOD

This prospective study was approved by Kocaeli University Non-interventional Clinical Researches Ethics Committee (Date: 20.07.2016, Decision No: KÜ-GOKAEK 2016). Before the procedure, each patient was informed about the indication, technique, and possible complications of CTL, and written informed consent was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between July 2017 and June 2020, patients with histopathologically proven breast cancer were evaluated for SLNB by the departments of General Surgery and Radiology. Histopathological diagnoses were confirmed by core-needle biopsy. Patients with pathologic axillary lymph nodes or distant metastases, inflammatory breast cancer, prior neoadjuvant chemotherapy, or known iodinated contrast allergy were excluded from the study. A clinically node-negative axilla was determined by the absence of palpable lymph nodes, the absence of sonographically suspicious lymph nodes, and/or the absence of metastatic lymph nodes confirmed by US-guided biopsy. The patients underwent CTL for axillary lymph node mapping in our CT unit before breast surgery, including SLNB with the BD method. The time interval between the CTL procedure and surgery was 45 minutes to 7 hours.

The CTL procedure was performed using the "Aquilion 64 helical CT scanner (Toshiba)". Pre-contrast CT images were obtained from the upper thoracic region to the axilla with the patient in a supine position and arms in a cranial direction. The technical parameters of the CT scan were as follows: "120 kV, 250 mA; slice thickness, 2mm; field of view, 350 x 450 mm; matrix, 512x512; table speed, 1.53 mm/0.5 s". The axial images were reconstructed with 0.5 mm pitch and 0.3 mm slice thickness.

Local anesthesia was administered using 8 mL of lidocaine hydrochloride 1%, with a 26-gauge needle at the 3, 6, 9, and 12 o'clock positions (2 mL each) subcutaneously on the areola. Then, 2 mL of iodinated contrast (Iohexol, Omnipaque®, 350mg/200 mL) was administered at the same positions on the areola subcutaneously, using a 26-gauge needle. To facilitate drainage of the contrast to the lymphatic ducts (LDs) and LNs, the breast was gently massaged from the areola towards the axilla for 60 seconds. The procedure was performed by two radiologists working at the same time to avoid any delay in contrast injection and massage. Three sets of CT scans were performed in the 1st, 3rd, and 5th minutes after contrast injection.

The images were automatically transferred to the workstation, and densities of the LNs were measured by carefully placing the range of interest to avoid the peripheral structures. 3D maximum intensity projection (MIP) images were used to define the LDs (**Figure 1**). The SLN was identified as the LN(s) to which the contrast medium in the LD(s) reached. If more than one enhanced LN was present, the SLN was detected by tracing the LDs. In cases where the ductal system was poorly visualized, the densities (HU) of the LNs on pre- and post-contrast images were measured, and the LN with the earliest contrast enhancement was considered as the SLN.

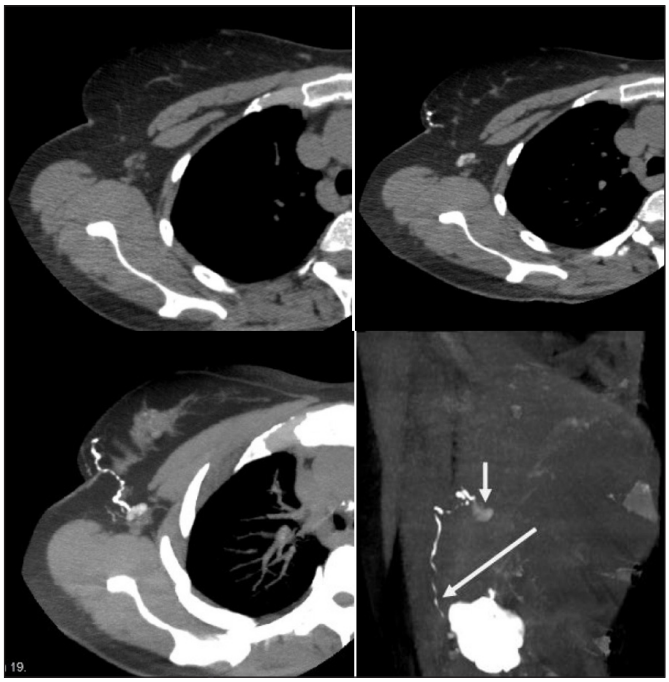

Figure 1. a-d. A 44-year-old female has invasive ductal carcinoma. She undergoes a CTL procedure, with precontrast (a) and 3rd minute postcontrast (b) axial images taken. An axial MIP (c) and 3D MIP (d) images are also obtained. The images show the contrast-enhanced lymphatic duct (long arrow) and the sentinel lymph node (short arrow).

After determination of the SLN(s), a metallic marker was placed on the skin over the determined LN(s) as a guide. The projection of the LN(s) onto the skin was marked over the CT plane light with a permanent pen, and the breast surgeon team was informed about the results. The CTL procedure lasted 20 to 45 minutes.

In the operating theater, 8 mL of methylene blue (Blumet, 100mg/10mL) was injected SC at the periareolar 3, 6, 9, and 12 o'clock positions (2 mL at each site) with a 26-gauge needle. After 5 minutes of massaging, all the blue-stained LNs in the axilla were excised. The LN(s) marked by CTL were also excised, even if they were not stained blue. Each excised LN was carefully noted to indicate which technique was used for its determination (BD, CTL, or both). In case of metastatic involvement reported by the Pathology Department, ALND was performed in the same setting.

Statistical Analysis

The CTL and BD techniques were compared for overall SLN detection rates as well as detection rates based on the presence of metastatic involvement in the LN(s), tumor location, and age of the patients. The statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) for Windows 20.0 program. The t-test was used to evaluate the data, with $p<0.05$ being considered statistically significant.

RESULTS

A total of 47 women (mean age: 50; range: 28-77) underwent CTL before breast surgery, including SLNB. Of these, 45 patients had early-stage (T1 or T2) invasive breast cancer, and 2 patients had ductal carcinoma in situ (DCIS) and underwent mastectomy. The histopathological diagnoses were invasive ductal carcinoma (n=42), invasive lobular carcinoma (n=3), and DCIS (n=2).

The 45 invasive cancers had a mean tumor diameter of 1.98 cm, ranging from 0.6 to 5.0 cm. The two patients with ductal carcinoma in situ had tumors measuring 10.5 cm and 1.5 cm, and SLNB was performed in both cases due to planned mastectomy. The location of the lesions was in the right breast in 25 patients, with 16 in the upper outer quadrant, 5 in the lower outer quadrant, 3 in the upper inner quadrant, and 1 retroareolar. In the left breast, 22 patients had lesions, with 12 in the upper outer quadrant, 3 in the lower outer quadrant, 3 in the upper inner quadrant, 1 in the lower inner quadrant, and 3 retroareolar.

During the surgery, 26 patients without metastatic axillary LNs underwent breast surgery and SLNB, while 21 patients had to undergo ALND, with 19 of them having metastatic SLNs. Two patients required ALND because SLN could not be detected by either method.

A comparison of the two methods in 47 patients showed that in 27 (57.5%) patients, the same lymph node (LN) was identified with both CTL and BD. In 12 (25.6%) patients, CTL failed to identify any LN while BD was successful. On the other hand, 6 (12.7%) patients had no LN detected by BD, but CTL found SLNs in 4 (8.5%) of them. In 2 of these 4 cases, the SLNB confirmed that the detected LNs were benign, thus avoiding unnecessary ALND thanks to CTL. However, in 2 (4.3%) patients, BD and CTL marked different LNs, and subsequent pathological examination showed that only the LNs identified by BD had metastatic involvement. As a result, the LNs identified by CTL in these 2 patients were not considered sentinel. Finally, in 2 (4.3%) patients, neither method was able to detect any LN, and ALND revealed benign axillary LNs.

The rates of detecting the SLNs using two different methods, BD and CTL, as well as the overall detection rate using either method or both, are presented (**Table 1**). These rates were compared based on the presence of metastatic involvement in the lymph nodes. The results showed that the rate of SLN detection was significantly higher with BD compared to CTL, with a P-value of 0.027. However, the higher detection rate when using at least one of the methods (BD and/or CTL) compared to BD alone was not statistically significant, with a P-value of 0.267.

Table 1. Comparison of the detection rates of SLNs according to metastatic LN involvement in CTL, BD and with at least one of the methods (BD and/or CTL).

	Benign (n=28)	Malignant (n=19)	Total (n=47)	P
CTL	20 (71.4%)	11 (57.9%)	31 (66.0%)	
BD	24 (85.7%)	17 (89.5%)	41 (87.2%)	0.027 (BD vs CTL)
BD and/or CTL	26 (92.9%)	19 (100.0%)	45 (95.7%)	0.267 (BD vs BD+CTL)

CTL: CT lymphgraphy; BD: Blue-dye method

According to the presence of metastatic LNs, the differences in detection rates of both methods were not statistically significant. With CTL, the detection rate of benign SLNs was higher than that of metastatic SLNs (P=0.366). With BD, the detection rate of malignant SLNs was higher than that of benign SLNs (P=1.00).

According to the detected LNs and LDs, CTL successfully identified SLNs in 31 (66.0%) of 47 patients. Of these 31 patients, both LDs and SLN were successfully imaged in 12 (38.7%) patients with CTL. In 19 (61.3%) patients in whom LDs could not be visualized, the first contrast-enhanced LN in the axilla was considered as the SLN. A total of 37 LNs were marked in 31 patients with CTL (1 in 28 patients, 2 in 2 patients, and 3 in 1 patient). In 16 of the 47 (34.0%) patients who underwent CTL, no LN could be marked because the contrast did not reach the axilla. A total of 46 LNs were blue-stained in 41 patients with BD (1 in 37 patients, 2 in 3 patients, and 3 in 1 patient). In 6 (12.8%) of the 47 patients who underwent BD, no LN was stained. In 4 of the 6 patients in whom no LN could be identified with the BD method, CTL was able to detect SLNs.

According to tumor location, the SLN detection rate of CTL and BD methods were 17 (60.7%) and 25 (89.3%) of 28 upper outer quadrant tumors and 5 (62.5%) and 7(87.5%) of 8 lower outer quadrant tumors, respectively. The performances of the two methods were similar in the retroareolar (3 of 4, 75.0%) and in the upper inner (5 of 6, 83.3%) and the lower inner (1 of 1, 100%) quadrants. The success of CTL in upper outer quadrant tumors (60.7%) was lower than the rest of the tumors (14 of 19, 73.7%), but this difference was not statistically significant (P=0.220). On the other hand, the success of BD in upper outer quadrant tumors (89.3%) was higher than the rest of the tumors (84.2%), with no statistical significance (P=0.674). Two SLNs that could not be detected by either method were in patients with DCIS in the left lower outer quadrant and invasive lobular carcinoma in the right upper outer quadrant. These patients underwent ALND after which no metastatic involvement was noted.

According to age, CTL was successful in 18 (90.0%) of 20 patients under 50 years of age and 13 (48.2%) of 37 patients 50 years and over. The higher rate of success in younger patients was statistically significant (P=0.001). The BD method was successful in 18 (90.0%) of 20 patients under 50 years of age and in 23 (85.2%) of 27 patients 50 years and over. The higher rate of success in younger patients was not statistically significant (P=0.378).

DISCUSSION

In our research, the success rate of detecting SLNs with the CTL method was 66.0%, which was lower than previous reports by Minohata et al. (24) who reported a 98.5% success rate, and Takahashi et al. (21) who reported a 96% success rate. The detection rate of SLNs with BD in our study was 87.2%, similar to previous reports. In a meta-analysis of 18 studies, Li et al. (25) reported a detection rate of 75-100%. The combination of CTL and BD methods improved the detection rate of SLNs from 87.2% to 95.7% in our study. Although this increase was not statistically significant (P=0.267), the results were similar compared to previous reports. Minohata et al. (24) reported that the SLN detection rate was 95% with only the BD method, but 99% with the addition of CTL. Similarly, Takahashi et al. (21) reported an increase in the detection of SLNs from 92% to 99% with the combination of CTL to the conventional BD technique.

Our study found that the SLN detection rate with CTL was higher in benign LNs (71.43%) compared to metastatic SLNs (57.9%), which was consistent with previous reports. Takahashi et al. (21) and Minohata et al. (24) also reported lower detection rates in metastatic LNs. The possible explanation for this failure in metastatic LNs may be the blockage of lymphatics by tumor cells or the development of alternative lymphatic pathways (26).

Our study found that with BD, benign SLNs were successfully detected by 85.7% and metastatic SLNs by 89.5%, which was not compatible with previous reports. Takahashi et al. (21) and Minohata et al. (24) reported a better rate of detection in benign SLNs than metastatic SLNs with BD.

Motomura et al. (23) used the size criteria for the differentiation of benign and metastatic LNs. A node larger than 5 mm in short-axis diameter on CTL was considered metastatic. Nakagawa et al. (14) described a typical pattern of metastatic LNs and LDs on CTL. According to this study, a stain defect in the LNs, as well as dilatation and stagnation of lymphatics, were signs of metastases. They reported 92.5% sensitivity, 88.6% specificity, and 89% accuracy with the criteria they defined. In a 12-year study, Yamamoto et al. (22) reported that SLNB disclosed 12% and 40% of micro- and macrometastasis, respectively, in LNs with filling defects. In LNs without any contrast filling defects, SLNB disclosed 5% and 7% micro- and macrometastasis, respectively. Due to the high rate of false negative and positive results, filling defects in LNs detected by CTL was not a reliable diagnostic criterion for the presence of metastasis. In our series, we ignored the presence of filling defects since the aim of CTL was to localize the SLN(s), not to differentiate benign and metastatic LN(s) (**Figure 2**).

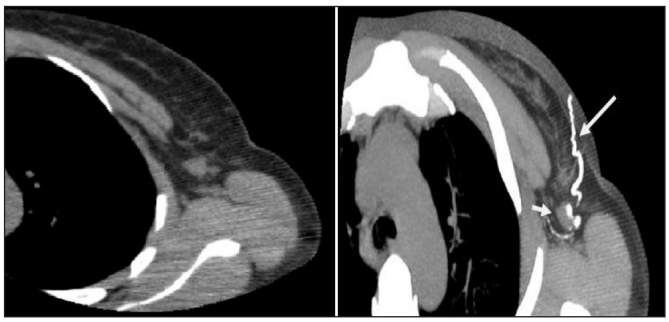

Figure 2. a-b. A 46-year-old female presents with invasive ductal carcinoma. SLN pathology is negative for metastasis. An axial precontrast image shows two radiologically benign lymph nodes (a). An axial postcontrast MIP image shows a filling defect in the larger lymph node (short arrow) and a contrast-filled lymphatic duct (long arrow) (b).

Identification of LDs enable a more accurate localization of SLNs (22). With the RILtechnique, LDs cannot be clearly identified as in BD or CTL methods. Yamamoto et al.(22) could image both LNs and LDs in 96% of the patients with CTL. In our study, both LDs and SLNs could be imaged in 12 (38.7%) patients with CTL, whereas in 19 (61.3%) patients only SLNs were imaged. The authors need more experience to develop their technical skills, since the success rate of SLN detection was lower in our initial cases.

Both CTL and BD methods could not perform a statistically significant difference, according to the location of tumors. CTL showed lesser success in the upper outer quadrant tumors (73.7%), compared to otherlocations

(60.7%).Similarly in a study with CTL, Minohata et al. (24) reported a lower detection rate of SLNs in upper outer quadrant tumors (96%),than other quadrant tumors (100%),without statistical significance(P=0.24). Success rate of BD in the upper outer quadrant (89.3%) was higher than in other locations(84.2%) in our study. However, Minohata et al. (24) reported that SLNs of tumors located in the upper outer quadrant (98%) could be detected less than other quadrant tumors(100%) with the BD method (P=0.29).

Minohata et al. (24) reported that CTL was more successful in patients older than 50-years-old (P=0.24). In our study both BD (P=0.378) and CTL (P=0.001) were more successful in younger patients. In the same study, they reported no statistically significant association between body mass index (BMI), tumor size, and success of CTL, either. In our study we did not study a possible correlation with BMI and tumor size.

There are different, relatively new radiological techniques other than CTL which may be an alternative to BD in SLNB. With MR lymphography using superparamagnetic iron oxide as contrast agent,97-100% detection rate of SLNs were reported (11,15).With US lymphography using sonographic contrast agents Sonazoid(Perfluorobutane) (17) and Sonovue (sulfur hexafluoride) (27), detection rates of 95% to 98% were reported. But these techniques need to be validated by larger series.

The limitations of this study is the relatively small number of patients and the relatively limited experience of the CTL operators. Breast surgeon team in the study group has been practising SLNB with BD technique for the last 14 years. However CTL procedure has been practiced since 2015 by the radiologists. SLNB with CTL has become popular since early 2000's especially in Japan. In our country it is not a frequent technique. In our institution, we have got promising results with our 3-year-experience.

CONCLUSION

The CTL is insufficient as a stand-alone method to determine SLNs, but may be a complementary method that increased the success of SLN detection when applied together with BD method. With increasing experience, it will provide better results for more accurate localization of SLNs. Studies with larger patient series will shed light on the subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kocaeli University Non-interventional Clinical Researches Ethics Committee (Date: 20.07.2016, Decision No: KÜ-GOKAEK 2016).

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 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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Bibliometric analysis of the 50 most cited articles on artificial intelligence for lung cancer imaging

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ABSTRACT

Aim: The use of machine learning has now become widespread in lung cancer. However, the research trend is still unclear. This study aimed to analyze the most influential publications on artificial intelligence (AI) for lung cancer.

Material and Method: A comprehensive PubMed and SCImago Journal and Country Rank (SJR) search was performed. The 50 most cited articles were recorded according to the citation numbers, the country and institute of articles, the name and metrics of the publishing journal, the year of publication, and the content of the articles.

Results: The citation numbers ranged from 24 to 628. Annual citations per article was between 1.47 and 104.6. The USA was the country with the most publications (n=22) followed by The Netherlands (n=9) and Peoples R China (n=5). The journal and institution that highly contributed to the 50 most cited articles were Radiology (n=5) and Harvard Medical School (n=5), respectively.

Conclusion: The importance of deep learning and AI in lung cancer imaging is increasing day by day. In this study, a detailed bibliometric analysis of the literature on AI in lung cancer imaging was performed. In addition, this bibliometric analysis informs researchers about current influential papers in this field, the characteristics of these studies, and potential future trends in the rapidly evolving field of AI in lung cancer screening.

Keywords: Artificial intelligence, bibliometric analysis, lung cancer

INTRODUCTION

Lung cancer is the most common type of cancer for decades and still causes more deaths worldwide in both sexes than any other type of cancer (1). As stated in Cancer Statistics 2020, the rate of 5-year survival in lung cancer is 19% (2). Most early-stage lung cancers have no obvious symptoms, and the patient is advanced when symptoms appear, resulting in a low overall rate of 5-year survival for advanced lung cancer (3). Because of the aggressive nature of lung cancer, early detection and intervention is vital. Thin section computed tomography (CT) is an efficient modality to screen high-risk groups. Computer-assisted diagnosis, invasive biomarkers, video-assisted thoracic surgery and fluorine-18 fluorodeoxyglucose positron emission tomography-CT (18F-FDG PET-CT) scanning are making important contributions to the prevention, early diagnosis and also treatment of lung cancer (4). Due to the widespread use of health and thin-section CT examinations in recent years, early diagnosis rate of lung cancer has increased (5). Early diagnosis is an important procedure to reduce deaths from lung cancer (6). To increase diagnostic efficiency, a computer-aided diagnosis (CAD) system was developed to assist physicians in interpreting medical imaging data (7,8), which has been cited as a useful second opinion for physicians (9). Standardizing the nodule follow-up in thorax CT scanning programs performed in high risk groups for lung cancer helps clinicians and radiologists in the early diagnosis of nodules with high cancer probability.

The traditional feature-based CAD task can be divided into three steps: nodule segmentation, feature extraction and selection, and clinical judgment inference (classification). For estimation of malignancy risk, measurements include the size, type, location, number and margin of nodule and emphysema finding on CT scans, and there are clinical variables such as patient's age, gender, timing of sampling, family history of lung cancer, and exposure to smoking. However, these features, although mostly subjective, often fail to

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provide a complete and quantitative description of the malignant nodule (6). The development of deep learning algorithms, especially convolutional neural networks, has led to further work to apply deep learning-based models to the CAD system to improve accuracy and reduce false positive rate and implementation time during lung tumor diagnosis (10,11).

Artificial intelligence (AI) also provides a different perspective in lung cancer-related research and allows exploration of the application of decision support mechanisms to facilitate precision oncology (6). In the context of oncology, AI is increasingly being researched and used for several different purposes (12). In recent years, the use of AI in cancer diagnosis has become widespread with the contributions of different fields such as medicine, computer science, mathematics and engineering, which is not limited to clinical practice (13).

Bibliometric analysis is an analysis based on evaluating the literature published on a particular subject (14). Citation frequency is used to determine how often a publication is cited by other researchers (15). It involves collating data to identify the most influential publications on this topic, identify trends in specific research areas, and identify potential gaps where further research is needed (14). The citation count of an article is an important objective indicator of how much credibility and attention it receives in the academic world (16).

The aim of this study was to analyze a list of the most cited publications on the use of AI in lung cancer imaging for clinicians and researchers. It also presents a detailed analysis of the evolution and change of trends in this area.

MATERIAL AND METHOD

This study was carried out as a retrospective bibliometric analysis and did not include human or animal subjects. So, ethical approval was not required for this bibliometric study.

The literature search of 50 most cited articles was performed using PubMed® database (search at: https://pubmed.ncbi.nlm.nih.gov/) (17), SCImago Journal and Country Rank (SJR) based on Scopus® data (Elsevier BV Company, GA, USA; search at https://www.scimagojr.com/) (18) and 2021 Journal Citation Reports® (search at: https://jcr.clarivate.com/jcr/home) (19). MeSH terms that was used for search included "Lung cancer, imaging" and "artificial intelligence".

The search was restricted to human study and English in article language. Research and review articles were included in the study. No publication year restrictions were made in the search. The research started on March 20, 2023. Publications whose full text was not available, were excluded. Articles that included at least one imaging modality (e.g., x-ray, CT, magnetic resonance imaging, ultrasound) were included in the study. Finally, 1563 articles were reached. The articles that did not meet the inclusion criteria, was excluded. 875 articles remained including research and review articles in English language (**Figure 1**). Articles were noted in order of citation numbers from highest to lowest in PubMed® database (17). Citation per year was calculated by dividing the total number of citations by the time elapsed until the year the article was published (20). Article type, publication year, author and article information, journal metrics, country and author institution information were recorded in an excel file. The institutions were provided by affiliations of first authors. The countries were noted according to the address stated by the first author. The impact factors were taken from the 2021 Journal Citation Reports® (19) and journals' h-index and SJR values were obtained from SCImago based on Scopus® data (Elsevier BV Company, GA,USA; search at https://www.scimagojr.com/) (18).

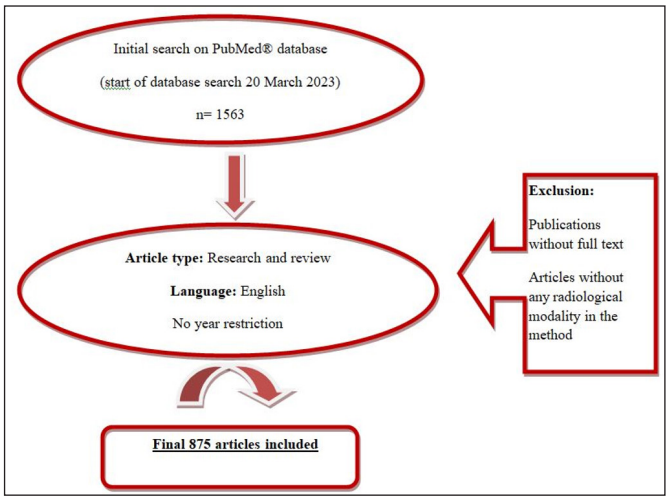

Figure 1. Literature search strategy - inclusion and exclusion criteria

For the data analysis, descriptive statistics were performed. No statistical tests were performed. In this study, the distribution of the literature on the use of AI in lung cancer by different years, countries, institutions and authors were evaluated. Therefore, numbers were used in statistical analysis without comparison between groups.

RESULTS

The information of the 50 most cited articles on AI for lung cancer were given in **Table 1**. The citation numbers ranged from 24 to 628 (mean: 71.56). Annual citations per article was between 1.47 and 104.6 (mean:12.62).

Table 1. The 50 most cited articles about artificial intelligence on lung cancer imaging

	Article type	Year	Citation number	Citation per year	First Author	Title	Journal
1	research	2017	628	104.6	van Griethuysen JJM	Computational Radiomics System to Decode the Radiographic Phenotype.	Cancer Res.
2	research	2015	379	47.3	Parmar C	Machine Learning methods for Quantitative Radiomic Biomarkers.	Sci Rep.
3	research	2019	184	46	Ardila D	End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography.	Nat Med.
4	review	2019	154	38.5	Bi WL	Artificial intelligence in cancer imaging: Clinical challenges and applications.	CA Cancer J Clin.
5	research	2017	144	24	Rios Velazquez E	Somatic Mutations Drive Distinct Imaging Phenotypes in Lung Cancer.	Cancer Res.
6	research	2018	140	28	Rajpurkar P	Deep learning for chest radiograph diagnosis: A retrospective comparison of the CheXNeXt algorithm to practicing radiologists.	PLoS Med.
7	research	2019	131	32.75	Nam JG	Development and Validation of Deep Learning-based Automatic Detection Algorithm for Malignant Pulmonary Nodules on Chest Radiographs.	Radiology.
8	research	2019	130	32.5	Xu Y	Deep Learning Predicts Lung Cancer Treatment Response from Serial Medical Imaging.	Clin Cancer Res.
9	research	2016	111	15.8	Setio AA	Pulmonary Nodule Detection in CT Images: False Positive Reduction Using Multi-View Convolutional Networks.	IEEE Trans Med Imaging.
10	research	2019	78	19.5	Trebeschi S	Predicting response to cancer immunotherapy using noninvasive radiomic biomarkers.	Ann Oncol.
11	research	2007	66	4.125	van Baardwijk A	PET-CT-based auto-contouring in non-small-cell lung cancer correlates with pathology and reduces interobserver variability in the delineation of the primary tumor and involved nodal volumes.	Int J Radiat Oncol Biol Phys.
12	research	2002	64	3.04	Hripcsak G	Use of natural language processing to translate clinical information from a database of 889,921 chest radiographic reports	Radiology.
13	research	2019	60	15	Beig N	Perinodular and Intranodular Radiomic Features on Lung CT Images Distinguish Adenocarcinomas from Granulomas.	Radiology.
14	research	2018	57	11.4	Lustberg T	Clinical evaluation of atlas and deep learning based automatic contouring for lung cancer.	Radiother Oncol.
15	research	2018	54	10.8	Hosny A	Deep learning for lung cancer prognostication: A retrospective multi-cohort radiomics study.	PLoS Med.
16	review	2020	52	17.3	Avanzo M	Radiomics and deep learning in lung cancer.	Strahlenther Onkol.
17	research	2017	50	8.33	Dou Q	Multilevel Contextual 3-D CNNs for False Positive Reduction in Pulmonary Nodule Detection.	IEEE Trans Biomed Eng.
18	research	2017	44	7.33	Wang S	Central focused convolutional neural networks: Developing a data-driven model for lung nodule segmentation.	Med Image Anal.
19	research	2019	43	10.75	Lou B	An image-based deep learning framework for individualizing radiotherapy dose.	Lancet Digit Health.
20	research	2006	43	2.52	Kuhnigk JM	Morphological segmentation and partial volume analysis for volumetry of solid pulmonary lesions in thoracic CT scans.	IEEE Trans Med Imaging.
21	research	2018	42	8.4	Nishio M	Computer-aided diagnosis of lung nodule classification between benign nodule, primary lung cancer, and metastatic lung cancer at different image size using deep convolutional neural network with transfer learning.	PLoS One.
22	research	2007	42	2.625	McNitt-Gray MF	The Lung Image Database Consortium (LIDC) data collection process for nodule detection and annotation.	Acad Radiol.
23	research	2010	41	3.15	Messay T	A new computationally efficient CAD system for pulmonary nodule detection in CT imagery.	Med Image Anal.
24	research	2017	41	6.83	Ciompi F	Towards automatic pulmonary nodule management in lung cancer screening with deep learning.	Sci Rep.
25	research	2011	41	3.42	Tan M	A novel computer-aided lung nodule detection system for CT images.	Med Phys.

Table 1. The 50 most cited articles about artificial intelligence on lung cancer imaging

	Article type	Year	Citation number	Citation per year	First Author	Title	Journal
26	research	2005	39	2.16	Suzuki K	Computer-aided diagnostic scheme for distinction between benign and malignant nodules in thoracic low-dose CT by use of massive training artificial neural network.	IEEE Trans Med Imaging.
27	research	2009	38	2.71	Ye X	Shape-based computer-aided detection of lung nodules in thoracic CT images.	IEEE Trans Biomed Eng.
28	research	2003	38	1.9	Suzuki K	Massive training artificial neural network (MTANN) for reduction of false positives in computerized detection of lung nodules in low-dose computed tomography.	Med Phys.
29	research	2009	37	2.64	Murphy K	A large-scale evaluation of automatic pulmonary nodule detection in chest CT using local image features and k-nearest-neighbour classification.	Med Image Anal.
30	review	2020	36	12	Chassagnon G	Artificial intelligence applications for thoracic imaging.	Eur J Radiol.
31	research	2020	36	12	Sim Y	Deep Convolutional Neural Network-based Software Improves Radiologist Detection of Malignant Lung Nodules on Chest Radiographs.	Radiology.
32	research	2020	36	12	Mu W	Non-invasive decision support for NSCLC treatment using PET/CT radiomics.	Nat Commun.
33	research	2016	35	5	Teramoto A	Automated detection of pulmonary nodules in PET/CT images: Ensemble false-positive reduction using a convolutional neural network technique.	Med Phys.
34	research	2006	35	2.05	Reeves AP	On measuring the change in size of pulmonary nodules.	IEEE Trans Med Imaging.
35	research	2017	31	5.16	Nibali A	Pulmonary nodule classification with deep residual networks.	Int J Comput Assist Radiol Surg.
36	research	2008	31	2.06	Pu J	Adaptive border marching algorithm: automatic lung segmentation on chest CT images.	Comput Med Imaging Graph.
37	research	2019	29	7.25	Liao F	Evaluate the Malignancy of Pulmonary Nodules Using the 3-D Deep Leaky Noisy-OR Network.	IEEE Trans Neural Netw Learn Syst.
38	research	2015	29	3.625	Ciompi F	Automatic classification of pulmonary peri-fissural nodules in computed tomography using an ensemble of 2D views and a convolutional neural network out-of-the-box.	Med Image Anal.
39	research	2019	29	7.25	Zhao W	Toward automatic prediction of EGFR mutation status in pulmonary adenocarcinoma with 3D deep learning.	Cancer Med.
40	research	2019	27	6.75	Baek S	Deep segmentation networks predict survival of non-small cell lung cancer.	Sci Rep.
41	research	2020	27	9	Sibille L	18F-FDG PET/CT Uptake Classification in Lymphoma and Lung Cancer by Using Deep Convolutional Neural Networks.	Radiology.
42	review	2020	27	9	Rogers W	Radiomics: from qualitative to quantitative imaging.	Br J Radiol.
43	research	2019	26	6.5	Linning E	Radiomics for Classification of Lung Cancer Histological Subtypes Based on Nonenhanced Computed Tomography.	Acad Radiol.
44	research	2018	26	5.2	Chen CH	Radiomic features analysis in computed tomography images of lung nodule classification.	PLoS One.
45	research	2020	25	8.33	Baldwin DR	External validation of a convolutional neural network artificial intelligence tool to predict malignancy in pulmonary nodules.	Thorax.
46	research	2006	25	1.47	Meyer CR	Evaluation of lung MDCT nodule annotation across radiologists and methods.	Acad Radiol.
47	research	2007	25	1.56	Reeves AP	The Lung Image Database Consortium (LIDC): a comparison of different size metrics for pulmonary nodule measurements.	Acad Radiol.
48	review	2016	24	3.42	Valente IR	Automatic 3D pulmonary nodule detection in CT images: A survey.	Comput Methods Programs Biomed.
49	research	2020	24	8	Dercle L	Identification of Non-Small Cell Lung Cancer Sensitive to Systemic Cancer Therapies Using Radiomics.	Clin Cancer Res.
50	review	2011	24	2	Shiraishi J	Computer-aided diagnosis and artificial intelligence in clinical imaging.	Semin Nucl Med.

There were 28 journals in which the 50 most cited articles were published. Of these 50 articles, 6 (12%) were reviews and 44 (88%) were research articles. The 50 most cited articles were published between 2002 and 2020 with almost half of them published in the 4-year period between 2017 and 2020. With 11 articles, 2019 was the year with the most article publications (**Figure 2**). This was followed by 2020 with 8 articles. Radiology published most articles on AI for lung cancer (n=5), followed by Academic Radiology (n=4), Medical Image Analysis (n=4) and IEEE Transactions on Medical Imaging (n=4). The impact factor of the most cited journals ranged from 3.408 to 286.13. H-index and SJR values of the most cited journals were given in **Table 2**.

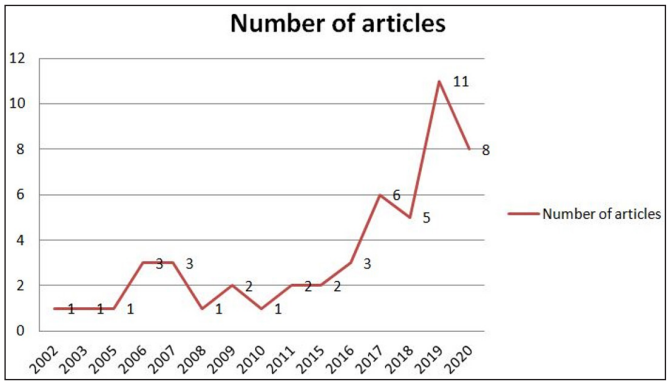

Figure 2. Number of articles by publication year

Table 2. The most cited journals with impact factor (IF), H index as provided by SCImago and SCImago Journal Rank (SJR) values

Journal	Number of articles	IF	H index	SJR
Radiology	5	29.146	307	4.59
Acad Radiol	4	5.482	100	1.02
Med Image Anal	4	13.828	143	4.17
IEEE Trans Med Imaging	4	11.037	233	4.05
Sci Rep	3	4.996	242	1.01
Med Phys	3	4.506	189	1.17
PLoS One	2	3.752	367	0.85
PLoS Med	2	11.613	242	4.18
IEEE Trans Biomed Eng	2	4.756	210	1.3
Clin Cancer Res	2	13.8	344	4.4
Cancer Res	2	13.312	466	3.08
Ann Oncol	1	51.77	258	8.59
Br J Radiol	1	3.629	110	0.8
CA Cancer J Clin	1	286.13	182	56.2
Cancer Med	1	4.711	65	1.14
Comput Med Imaging Graph	1	7.422	82	1.49
Comput Methods Programs Biomed	1	7.027	115	1.33
Eur J Radiol	1	4.531	119	1.01
IEEE Trans Neural Netw Learn Syst	1	14.255	221	4.22
Int J Comput Assist Radiol Surg	1	3.408	53	1
Lancet Digit Health	1	36.615	30	6.02
Nat Commun	1	17.7	410	4.85
Nat Med	1	87.241	576	24.16
Radiother Oncol	1	6.901	163	1.95
Semin Nucl Med	1	4.802	91	1.09
Strahlenther Onkol	1	4.033	72	0.92
Thorax	1	9.203	231	2.31
Int J Radiat Oncol Biol Phys	1	8.013	257	1.9

There were 13 different countries in the 50 most cited articles.The USA was the leading publication country (n=22), followed by The Netherlands (n=9) and Peoples R China (n=5) (**Figure 3**).

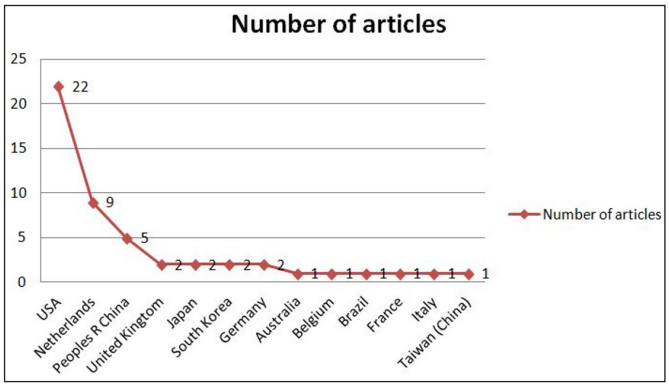

Figure 3. Number of articles by countries (according to address stated by the first author)

There were 36 different institutions in the 50 most cited article list. Harvard Medical School contributed the highest number of articles (n=5), followed by Maastricht University (n=4), Radboud University Medical Center (n=3), and the University of Chicago (n=3) (**Table 3**).

Table 3. The affiliations of the first authors by number of articles

Institution	Number of articles
Harvard Medical School	5
Maastricht University	4
Radboud University Medical Center	3
the University of Chicago	3
Columbia University	2
Cornell University	2
Stanford University	2
La Trobe University	1
Université Paris Descartes	1
University of Dayton	1
Case Western Reserve University	1
Centro di Riferimento Oncologico di Aviano (CRO) IRCCS	1
China Medical University Hospital	1
David Geffen School of Medicine at UCLA	1
Digital Technology and Innovation Division, Siemens Healthineers	1
Fujita Health University	1
Google AI	1
H. Lee Moffitt Cancer Center and Research Institute	1
Huadong Hospital Affiliated to Fudan University	1
Kyoto University	1
Medicsight PLC	1
MeVis-Center for Medical Visualization and Diagnostic Systems	1
Netherlands Cancer Institute	1
Nottingham University	1
Seoul National University Hospital and College of Medicine	1
Shanxi DAYI Hospital	1
The Chinese University of Hong Kong	1
Tsinghua University	1
Universidade Federal do Ceará	1
University Hospital Münster	1
University Medical Center, Utrecht	1
University of Chinese Academy of Sciences	1
University of Iowa	1
University of Michigan	1
Vrije Universiteit Brussel	1
Yonsei University College of Medicine	1

DISCUSSION

AI has become widespread in lung cancer imaging. Especially in last years, the number of related publications have increased. However, bibliometric analyzes aimed at assessing research trends regarding the role of AI in lung cancer imaging are still lacking in the literature. To the best of our knowledge, this bibliometric analysis is the first study on AI in lung cancer imaging.

In this bibliometric analysis, USA was the most productive country consistent with some studies on AI for cancer detection (13) and AI for radiotherapy in non-small cell lung cancer (21). In these two publications (13,21), the second most productive country was China. Differently, in this study, the Netherlands was the second most productive country. In a study conducted for the h-indexes of countries and using the Essential Science Indicators data (22), among the 40 countries evaluated, the USA had the highest h-index value of 749. This may be the result of the USA being able to allocate funds and resources to scientific research through its economic strength. It also gives information about the influence of developed countries in the conduct of scientific studies (23). Consistent with the result of this study, data from another study (24) showed that lung cancer radiomic research was predominantly concentrated in the USA, China, the Netherlands, and other countries. Some countries such as the USA and the Netherlands have undertaken many pioneering work based on theoretical and technological leadership. Some countries such as China, are generating abundant clinical data based on large numbers of cases, combined with advanced computer technology, contributing to important practical application outcomes. Therefore, current relevant research is relatively concentrated in the above-mentioned countries and research institutions, but collaborative research in this area is relatively extensive and many authors have participated in international collaboration (24).

In this study, the number of citations in 2019 and 2020 was higher than in other years. With the breakthroughs in AI technology, it is an expected result that the publication numbers will increase in the last few years depending on current trends. The fact that 2019 was the most productive year may be associated with the bibliometric analysis of the 50 most cited articles. The length of time elapsed since the publication of the article plays an important role in increasing citation numbers. Considering all the data in this study, the regular increase in the number of articles draws attention in recent years.

The fact that Radiology, Academic Radiology and Medical Image Analysis are the journals that highly contributed to 50 most cited articles is a result of radiology-based literature review.

Among the imaging modalities used in the studies, CT, PET-CT and radiomics were predominant. The increasing use of PET-CT for cancer staging, technological advances in PET-CT imaging and the discovery of new radiotracers, and clinical use of hybrid and molecular imaging modalities reflect the growing interest in PET-CT (25-28). In Liang et al.'s (24) literature analysis, radiomics were reported to be promising for lung cancer. In this study, articles using these imaging modalities were commonly encountered in the list of 50 most cited articles.

Yaxley et al. (28) stated it is not surprising that studies focusing on cancer detection and staging had the highest citation numbers, they also reported that it was interesting to notice the lack of studies on lung cancer imaging. Based on this lack in the literature, this study would be useful and contribute to the literature. However, there were some limitations of this study. It is an advantage of the study that it is not limited to a single database in the analysis of bibliometric data. However, being a single observer in the study is a limitation. A second limitation is that with the rapid development of AI technology, new publications are brought to the literature, so this study reflects the current data. As the third limitation, the publications that were not indexed in PubMed® could not be evaluated.

CONCLUSION

To the best of our knowledge, this is the first bibliometric analysis on AI in lung cancer imaging. This study will be a guide for future research. For researchers who want to work on this topic, it will be an important resource for a comprehensive literature review on research on AI in lung cancer imaging. Thus, the field of AI, which is developing day by day, will be able to develop with further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out as a retrospective bibliometric analysis and did not include human or animal subjects. So, ethical approval was not required for this bibliometric study.

Informed Consent: Not applicable.

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 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 Hashimoto's thyroiditis and vitamin D and the inflammatory marker platelet-to-lymphocyte ratio

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ABSTRACT

Aim: Hashimoto's thyroiditis (HT) is a chronic autoimmune-mediated disease that leads to overt hypothyroidism. Vitamin D is essential for immunity. This study examines possible impacts of vitamin D on the progression of HT and evaluates the use of platelet-lymphocyte ratio (PLR) as an indicator of its relationship with the inflammatory process.

Material and Method: This is a retrospective case-control study, consisting of 60 individuals with HT and 40 healthy controls. Thyroid function tests, thyroid antibodies, vitamin D levels, erythrocyte sedimentation rate (ESR), parameters of complete blood count and C-reactive protein (CRP) levels were scanned retrospectively using participants' medical files between September 2018 and March 2019. Platelet count was divided by lymphocyte count to determine PLR.

Results: HT patients had both considerably lower median vitamin D levels and higher percentages of vitamin D deficiency than the controls [12.08 (8.79–17.00) vs. 20.09 (20.00–34.00) and 80% vs. 22.5%, respectively, $p<0.001$). Vitamin D deficiency was also higher within the hypothyroid HT group than in the euthyroid HT group ($p<0.001$). The vitamin D levels of HT patients with subclinical hypothyroidism were lower than those with euthyroidism ($p<0.004$). The study groups showed no differences regarding CRP levels, higher levels of ESR were reported only in the overt hypothyroid patients ($p=0.001$), and higher PLRs were found in those euthyroid HT patients. Vitamin D was negatively correlated with TSH and anti-thyroid peroxidase (anti-TPO) levels ($r=-0.294$, $p=0.023$; $r=-0.281$, $p=0.030$, respectively). A positive correlation existed between TSH and anti-TPO ($r=0.411$, $p=0.001$) and ESR ($r=0.365$, $p=0.002$), but TSH and PLR were negatively correlated ($r=-0.390$, $p=0.002$).

Conclusion: According to these findings, vitamin D may play a role in the transition to the hypothyroid phase in HT patients, and thus, vitamin D replacement may inhibit this progression. Moreover, our results indicate that PLR may not be a good inflammatory indicator for vitamin D-deficient HT patients.

Keywords: Hashimoto's thyroiditis, vitamin D, platelet lymphocyte ratio, autoimmune thyroiditis, hypothyroidism, inflammation

INTRODUCTION

Hashimoto's thyroiditis (HT) may lead to overt hypothyroidism at a rate of approximately 5% every year (1,2). Environmental and genetic factors are thought to play a vital role in this chronic autoimmune-mediated disease, but the etiology is unclear. A better explanation of the underlying causes and factors that influence the progression to the hypothyroid stage can significantly benefit efforts to prevent and control the disease.

Vitamin D is essentially formed in the skin. It performs regulatory functions for the expression of more than 200 genes directly or indirectly (3). Vitamin D primarily maintains the homeostasis in calcium and phosphorus and regulates the metabolism of bone. However, the widespread existence of vitamin D receptors (VDR) in various cells and tissues throughout the body indicates that vitamin D might carry out additional functions beyond bone tissue (4). It has been shown that this type of vitamin has a chief role in adaptive and innate immunity (5). Vitamin D-deficient individuals are inclined to have a higher incidence and greater severity of autoimmune disorders (6). While several studies suggest that autoimmune thyroid diseases and deficiency of vitamin D are associated, how low vitamin D levels affect HT remains unclear (7,8).

Neutrophil, lymphocyte, and platelet measurements are inexpensive and easily measurable indicators for inflammation in various diseases. While neutrophil numbers increase and lymphocytes decrease in stress

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states, thrombocytosis is observed in inflammation (9). The neutrophil-to-lymphocyte ratio (NLR) increases in autoimmune thyroid diseases (AITD) (10). Similarly, some studies detected high platelet-to-lymphocyte ratios (PLR) among patients with AITD (11-14).

The study examines the probable influence of vitamin D on the clinical progression of HT patients and explores the use of PLR as an indicator of its relationship with the inflammatory process.

MATERIAL AND METHOD

This retrospective case-control study was conducted in the internal medicine and endocrine outpatient clinics of a tertiary referral hospital. The study protocol was in accordance with the Declaration of Helsinki. The researchers received ethics committee approval of the Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 30.05.2019, Decision No: 32/2019). The data on patient and control groups were collected through retrospective scanning of the medical records of the cases from September 2018 through March 2019. The study included one hundred participants, consisting of 60 individuals with HT (20 with euthyroidism, 20 with subclinical hypothyroidism, and 20 with overt hypothyroidism) and 40 healthy controls. The participants were matched for body mass index (BMI), age, and gender. HT was diagnosed based on the findings of high titers of anti-thyroglobulin (anti-TG) antibodies or anti-thyroid peroxidase (anti-TPO), followed by confirmation of thyroiditis by thyroid ultrasound examination. HT patients were classified according to thyroid function tests. While thyroid function tests were normal and only those with high thyroid antibodies were classified as euthyroid, patients with increased thyroid stimulating hormone (TSH) levels and normal levels of free triiodothyronine (fT3) and free thyroxine were diagnosed with subclinical hypothyroidism. Overt hypothyroidism was defined as having both low fT3 and/or fT4 levels as well as high TSH levels. The study included individuals between the ages of 18 and 65. Pregnant women, individuals with acute or chronic infections, chronic illnesses such as hypertension, diabetes mellitus, kidney disease, cardiovascular disease, liver disease, parathyroid gland disorders, smokers, and those who consume alcohol were excluded from the study. Individuals who have taken vitamin D medications or supplements which influence the metabolism of vitamin D and those who use any thyroid hormone replacement, immunosuppressive agents, anti-inflammatory drugs, or antibiotics were also not included in the study.

Age, gender, and BMI of each participant, 25(OH) vitamin D3, thyroid function tests, thyroid antibody levels, leukocyte, lymphocyte, neutrophil, and platelet counts, C-reactive protein (CRP) values, and erythrocyte sedimentation rate (ESR) were recorded from the medical files. Vitamin D levels were categorized based on the following criteria: levels of ≥30 ng/mL were considered sufficient, levels between 20 ng/mL and 30 ng/mL as insufficient, and levels below 20 ng/mL as vitamin D-deficient.

Complete blood count parameters (leukocytes, neutrophils, lymphocytes, and platelets) were analyzed by the auto analysis method on the Couter LH 780 Analyzer device from the blood taken into the tube with ethylenediamine tetraacetic acid (EDTA) anticoagulant. The platelet count was divided by the lymphocyte count to calculate PLR. Anti-TG and Anti-TPO antibodies, fT3, fT4, and TSH were quantified by means of the electrochemiluminescence method on a Roche Cobas 8000 chemistry analyzer (Rotkreuz, Switzerland). Tandem gold liquid chromatography-tandem mass spectrometry (Zivak Technologies, Turkey) was used for 25 (OH)D3 measurements and evaluated using the Dvit-Dia Source kits through the radioimmunoassay method.

Statistical Analyses

The data analyses were fulfilled through the SPSS version 23.0 (IBM Corp., Armonk, NY). The descriptive statistics examined within the scope of the study consisted of mean, median (interquartile range), standard deviation, percentiles, and number of cases. For study group comparisons, the Mann-Whitney U test and Student's t-test were utilized. Furthermore, ANOVA and the Kruskal-Wallis test were utilized to compare more than two groups according to the Kolmogorov-Smirnov normality test. Fisher's exact chi-square and Pearson's chi-square tests were employed to analyze categorical data. Pearson and Spearman correlation analyses were performed for correlations. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The sample consisted of 60 HT patients (20 euthyroid, 20 subclinical, and 20 overt hypothyroid) and 40 healthy controls. The groups showed similarities in gender, age, and BMI. Significantly lower median levels of vitamin D were detected in the HT group [12.08 (8.79–17.00) vs. 20.09 (20.00–34.00), $p < 0.001$]. Although the percentages of vitamin D sufficiency and insufficiency were higher in the control participants than those with HT (50%, 27.5% vs. 6.7%, 13.3%, $p<0.001$), the percentage of vitamin D deficiency was higher among participants with HT (22.5% vs. 80%, $p<0.001$). While the two groups did not display any statistical differences in leukocytes, neutrophils, lymphocytes, platelets, MPV, PLR, or CRP levels (all $p > 0.05$), ESR values in the HT group were detected to be significantly higher than in the control group ($p=0.01$) (**Table 1**).

According to the subgroup analysis, the comparison of the HT subgroups and the control patients did not reveal any statistical difference in age, gender, or BMI (**Table 2**). Vitamin D levels were statistically lower among the participants in all the subgroups of HT compared to the controls (p<0.001) (**Figure 1a**). Despite lower vitamin D levels in the hypothyroid HT groups than in the euthyroid HT groups, a significant difference was only uncovered between subclinical hypothyroid HT and euthyroid HT groups (p=0.004). The patients with euthyroid, subclinical, and hypothyroid HT were observed to be vitamin D-deficient more frequently than the control patients (90%, 90.0%, 60.0% vs. 22.5% respectively, p<0.001) (**Figure 1b**). Vitamin D deficiency was also higher within the hypothyroid HT groups than in the euthyroid HT group (p<0.001). Although the euthyroid HT patients had a higher level of PLR than the overt (p=0.002) and subclinical hypothyroid HT groups (p<0.001), no difference was found between this group and the controls (**Figure 2**). The CRP levels did not vary between the study groups; ESR was higher only in the overt hypothyroid HT group (p=0.001). The study groups displayed no differences in leukocytes, neutrophils, lymphocytes, platelet counts, and MPV (**Table 2**).

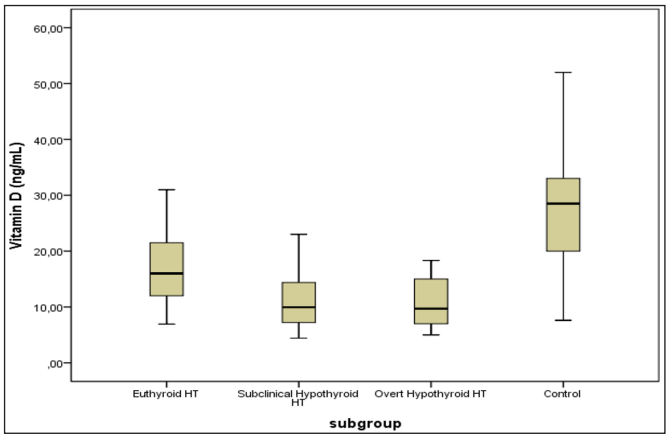

Figure 1a. Vitamin D levels in groups

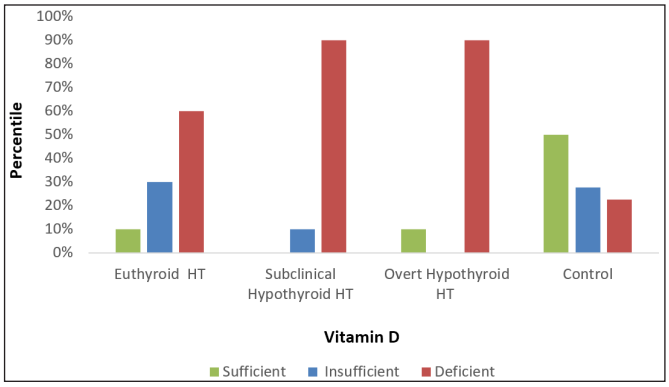

Figure 1b. Vitamin D deficiency rates in groups

Table 1. Comparison of clinical and laboratory characteristics between Hashimoto's thyroiditis and control groups

	HT (n:60)	Control (n:40)	P
Age(years)	45.50 (32.00-57.25)	47.61 (37.25-57.50)	0.394
Female/Male (n)	42/12	32/8	0.604
BMI (kg/m2)	28.22±1,83	28.21±1,74	0.742
TSH (µU/L)	5.00 (3.00-10.88)	1.85 (1.28 -3.17)	<0.001
fT3 (ng/L)	2.97±0.53	3.23±0.45	0.416
fT4 (ng/dL)	1.01±0.32	1.26±0.13	<0.001
Anti-TPO (IU/mL)	194 (63 – 447)	12.5 (10-13)	<0.001
Anti-TG (IU/mL)	238 (31-476)	10(10-14)	<0.001
25(OH)D3 (ng/mL)	12.00 (8.79-17.00)	29.09 (20.00-34.00)	<0.001
Calcium (mg/dL)	8.85 (8.67-9.33)	9.14 (8.84-9.37)	0.064
Phosphorus (mg/dL)	3.20 (2.97-3.51)	3.69 (3.33-4.00)	0.001
Leukocyte (10^3/µL)	6.57 (5.62-7.69)	6.65 (5.32-8.22)	0.961
Neutrophil (10^3/µL)	3.56 (2.70-4.49)	3.96 (2.83-4.69)	0.497
Lymphocyte (10^3/ µL)	2.20 (1.88-2.54)	2.27 (1.81-2.81)	0.869
Platelet (10^6/ µL)	296.50 (227.00-334.25)	266.00 (235.50-339.00)	0.655
MPV	10.64±0 .75	10.71±0.95	0.281
PLR	123.57 (99.39-147.73)	129.52 (91.93-161.73)	0.688
ESR (mm/s)	6.00 (4.00-16.00)	4.00 (2.25-7.50)	0.01
CRP (mg/dL)	1. 35 (0.60-2.55)	1.65 (0.60-4.19)	0.358
Sufficient (n, %)	4 (6.7%)	20 (50%)	
Vitamin D Insufficient (n, %)	8 (13.3%)	11 (27.5%)	<0.001
Deficient (n, %)	48 (80%)	9 (22.5%)	

HT, Hashimoto's thyroiditis; BMI, body mass index; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; TG, thyroglobulin; 25(OH)D3, 25-hydroxyvitamin D; PLR, platelet-to- lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Data were expressed as mean±standard deviation and median (interquartile range). P <0.05 was considered significant.

Table 2. Comparison of laboratory parameters in patients with euthyroid, subclinical hypothyroid, and overt hypothyroid Hashimoto's thyroiditis

	Euthyroid HT (n:20)	Subclinical Hypothyroid HT (n:20)	Overt Hypothyroid HT (n:20)	P
TSH (µU/L)	2.06 (1.61-3.01)[b,c]	5.0 (4.38-7.10)[a,d]	17.21 (8.96-54.00)[a,d]	<0.001
fT3 (ng/L)	3.15±0.58[c]	3.03±0.40	2.72±0.52[a,d]	0.003
fT4 (ng/dL)	1.14±0.19[c]	1.16±0.15[c]	0.66±0.23[a,b,d]	<0.001
Anti-TPO (IU/mL)	125 (34-248)	177 (62-553)[d]	349 (165-570)[d]	<0.001
Anti-TG (IU/mL)	198 (29-341)[d]	278 (31-832)	213 (22-932)[d]	<0.001
25(OH)D3 (ng/mL)	16.00 (12.00-21.75)[b,d]	9.95 (6.90-14.55)[a,d]	10.00 (7.29-15.90)[d]	<0.001
PLR	148.90 (126.90-164.74)[b,c]	114.55 (98.23-125.81)[a]	110.77 (87.08-133.52)[a]	0.006
ESR (mm/s)	4.00 (3.00-7.75)	6.50 (4.00-16.25)	12.00 (4.00-18.00)[d]	0.003
CRP (mg/dL)	1.40 (0.45-1.77)	1.15 (0.50-2.75)	1.55 (0.80-4.45)	0.380

HT, Hashimoto's thyroiditis; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; TG, thyroglobulin; 25(OH)D3, 25-hydroxyvitamine D3; PLR, platelet-to- lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Data were expressed as mean ± standard deviation and median (interquartile range). Letter a denotes a statistically significant difference with euthyroid HT; b denotes a significant difference with subclinical hypothyroid HT; c denotes a significant difference with overt hypothyroid HT; and d denotes a difference with the control group. P <0.008 was considered significant according to the Bonferroni correction.

Table 3. Correlation analysis of parameters in the HT group

	Vitamin D		PLR		ESR		CRP	
	r	p	r	p	r	p	r	p
TSH	-0.294	0.023	-0.390	0.002	0.365	0.004	0.231	0.076
fT3	-0.164	0.211	0.709	0.547	-0.240	0.065	-0.129	0.325
fT4	0.054	0.684	0.171	0.192	-0.179	0.170	-0.261	0.044
Anti-TPO	-0.281	0.030	-0.054	0.683	0.191	0.145	0.237	0.068
Anti-TG	-0.201	0.124	-0.074	0.576	0.144	0.273	0.104	0.431
Vitamin D	1.0		0.068	0.605	-0.190	0.146	-0.175	0.180
PLR	0.068	0.605	1.0		0.045	0.734	0.175	0.180
ESR	-0.190	0.146	0.045	0.734	1.0		0.570	<0.001

TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TPO, thyroid peroxidase; TG, thyroglobulin; 25(OH)D3, 25-hydroxyvitamine D3; PLR, platelet-to- lymphocyte ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

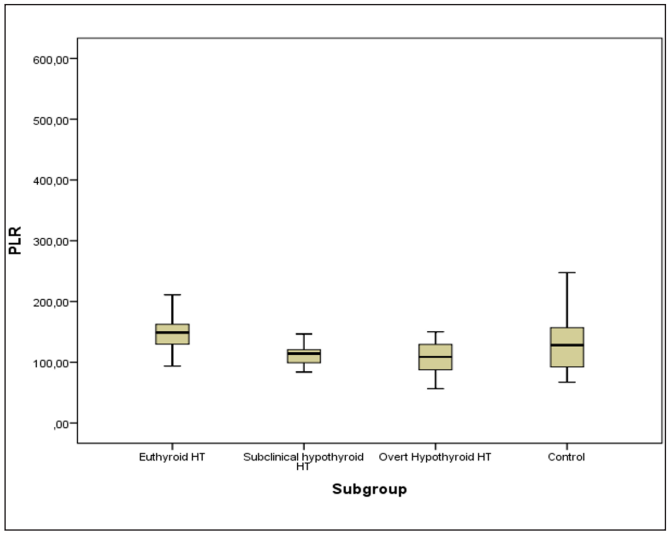

Figure 2. Platelet-to-lymphocyte ratios in groups

According to the correlation analysis, vitamin D levels were correlated with TSH and Anti-TPO levels in a negative direction (r=−0.294, p=0.023; r=−0.281, p=0.030, respectively). A positive correlation existed between TSH and anti-TPO (r=0.411, p=0.001) and ESR (r=0.365, p=0.002), but TSH and PLR were negatively correlated (r=−0.390, p=0.002) (**Table 3**).

DISCUSSION

The HT group had significantly lower amounts of vitamin D and higher prevalence of vitamin D deficiency than the controls in this study. Additionally, vitamin D deficiency was also found more frequently among the hypothyroid groups. HT patients with subclinical hypothyroidism displayed the lowest vitamin D levels. The study groups showed no differences regarding CRP levels, higher levels of ESR were observed only in the overtly hypothyroid HT group, and higher PLRs were found in those euthyroid HT patients. Vitamin D levels were negatively correlated with TSH and Anti-TPO. A positive correlation existed between TSH and anti-TPO and ESR, but TSH and PLR were negatively correlated.

It has recently been suggested that autoimmune diseases might be affected by vitamin D due to its essential role as an immune regulator (15). Studies have shown that vitamin D induces regulatory T lymphocytes, it decreases pro-inflammatory Th-1, Th-9, and Th-17 lymphocytes, and also suppresses the secretion of immunoglobulins from B lymphocytes (15,16). Most immune system cells harbor vitamin D receptors and express 1-alpha hydroxylase (CYP27B1). Active vitamin D synthesized

by this enzyme reduces the expression of the major histocompatibility complex class II on the surfaces of antigen-presenting cells, thereby making these cells more tolerant (15).

The pathophysiology of HT is mainly explained by an imbalance between T helper cells (CD4) and suppressor T cells (17,18). In this way, these cells can cooperate and activate B lymphocytes. Moreover, the production of various cytokines, such as interferon-gamma, by T helpers leads to the expression of MHC class II surface HLA-DR antigens not previously present in thyrocytes. This sensitizes the thyrocytes to immunological attack. Additionally, the production of thyroid antibodies by activated B lymphocytes further contributes to the autoimmune response. As we mentioned earlier, individuals with autoimmune thyroid disease are more likely to have lower levels of vitamin D and a higher prevalence of vitamin D deficiency (6). Furthermore, VDR gene polymorphisms are related to a raised risk of autoimmune thyroid disease (19,20). However, some studies detected no differences between the HT patients and the controls with respect to vitamin D levels (7,8). While Tamer et al. (21) observed lower vitamin D and a higher rate of vitamin D insufficiency among HT patients, there were no differences concerning vitamin D in euthyroid, subclinical hypothyroid, or overt hypothyroid HT groups. Likewise, another study revealed that lower vitamin D in the HT groups, and active vitamin D levels were similar to the control group (22). Consistent with most of the literature, our study showed that HT patients had lower vitamin D levels and more frequently suffered from vitamin D deficiency. Patients with subclinical hypothyroidism had significantly lower vitamin D than those with euthyroid HT. Moreover, vitamin D deficiency was more common in our patients with subclinical or overt hypothyroidism than in euthyroid HT patients. Vitamin D levels also had negative correlations with both TSH and anti-TPO levels. This made us think that vitamin D deficiency might influence the progression to the hypothyroid stage, and thus, the replacement of vitamin D may prevent this clinical course. The lack of expected differences in the levels of vitamin D between subclinical and overt hypothyroid groups may be due to variances in VDR gene polymorphism and individual 1-alpha hydroxylase activity.

Platelets significantly affect the regulation of immunity, inflammation, and hemostatic function (23). Although immune thrombocytopenia may be observed in some autoimmune thyroid patients, reactive thrombocytosis was found in the HT population (24,25). After the activation of platelets, various platelet-derived prothrombotic and pro-inflammatory factors, especially P-selectin, are synthesized and released from their granules. Platelets can bind to the inflamed endothelium and collect circulating leukocytes through these factors, enhancing platelet-leukocyte aggregation and thereby initiating an inflammatory reaction in the injured location (26). Inflammatory factors, including TNF-alfa, can also activate thrombopoietin secretion, which increases platelet production (27). Additionally, the stimulation of platelet activation and adhesion by these factors leads to the formation of a greater number of platelet-leukocyte aggregates, further promoting the progression of immune inflammation and creating a vicious circle. In the current study, PLR was similar to the controls but higher only in euthyroid HT patients than those with hypothyroid HT. Moreover, no differences existed between the groups in MPV, one of the platelet activation indicators. Even though the groups did not show any differences with regard to the CRP levels, ESR was only higher in the overtly hypothyroid HT patients. The levels of TSH were correlated with PLR in a negative direction and with anti-TPO and ESR in a positive direction. However, since different inflammatory parameters were increased in euthyroid and overt hypothyroid HT patients, we thought that PLR was not a good inflammatory indicator for our HT patients with vitamin D deficiency. We think other asymptomatic or unknown infectious or inflammatory processes accompanying the participants may contribute to the lack of expected differences in PLR.

The present study has certain limitations. Although the inclusion of only newly diagnosed patients in the same season is advantageous for the study, relying on retrospective data from medical records reduces the explanatory power of the study. Additionally, it may not be possible to identify all inflammatory conditions that could influence PLR values in participants.

CONCLUSION

Our study revealed that HT patients had lower vitamin D and higher vitamin D deficiency than the controls. Lower amounts of vitamin D were found in subclinical hypothyroid HT patients than the euthyroid HT patients. It can be concluded based on the study results that vitamin D may play a role on the transition from the euthyroid phase to the hypothyroid phase, and the replacement of vitamin D could inhibit the progression to hypothyroidism. Moreover, our results indicate that PLR might not be a good inflammatory marker for vitamin D-deficient HT patients. In order to improve our understanding of how significant vitamin D is in the onset and progression of HT, randomized controlled trials with extended follow-up periods are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Clinical Researches Ethics Committee of Ankara Training and Research Hospital (Date: 30.05.2019, Decision No: 32/2019).

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 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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Effect of tocilizumab in subarachnoid hemorrhage-induced cerebral vasospasm of experimental rats

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ABSTRACT

Aim: This study aimed to evaluate the effects of tocilizumab (TCZ), a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1k subclass, on vascular morphological changes, endothelial apoptosis, and the levels of pro-inflammatory and apoptotic cytokines, such as IL-6, tumor necrosis factor-alpha (TNF-α), caspase-3, Bcl-2 associated X-protein (BAX), and vascular endothelial growth factor (VEGF) in a rat SAH model.

Material and Method: The rats were randomly assigned (animal study) to 4 groups KONÜDAM Experimental Animal Research Center, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey; 15/03/2019): (1) normal control (without SAH); (2) SAH (without treatment); (3) SAH treated with saline (SAH + Sal.); and (4) SAH treated with TCZ (SAH + Toc.). The tissues were measured using enzyme-linked immunosorbent assay (ELISA) kits. A series of brain and basilar artery sections were categorized into several subgroups for hematoxylin and eosin (H&E) staining, immunohistochemistry, and Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining.

Results: The levels of caspase, BAX, and IL-6 in the SAH + TOC group were significantly lower than in other groups. TCZ treatment significantly increased the lumen of the basilar artery compared with that in the SAH and SAH + SAL groups without treatment (p=0.002 and p=0.004 respectively). SAH increased the apoptotic index in the endothelium compared with TCZ treatment (p=0.027) groups.

Conclusion: It can be concluded that TCZ is safe and effective for treating experimental SAH. The results reveal clearly experimental evidence for the potential clinical application of TCZ in SAH patients.

Keywords: Subarachnoid hemorrhage, tocilizumab, vasospasm

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a major cause of cerebrovascular morbidity and mortality in young patients. According to De Rooij et al. (1), the incidence of SAH is ~9 per 100,000 person-years, with a large regional variability (2). One of the major complications following SAH is vasospasm, which reflects the mechanistic concept of arterial narrowing that results in perfusion deficits and ischemia and, ultimately, into infarctions (1). Around one-third of patients with SAH have vasospasm, and nearly 50% of them develop cerebral ischemia (3). Cerebral vasospasm is characterized by the prolonged but reversible contraction of the cerebral arteries and significant morphological changes occurring in the arterial wall, such as intimal hyperplasia, luminal narrowing, and endothelial apoptosis (4). The pathophysiology of SAH is complex and involves genetic factors (5), microthrombi formation (6), and (neuro) inflammation (7). Elevated inflammatory responses mediated by increased cytokine release in the cerebrospinal fluid (CSF) and plasma are correlated with adverse clinical outcomes in patients with SAH. The proinflammatory cytokines involved in SAH include interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-alpha (TNF-α) (1,8). IL-6 is a central player in physiological neuronal and glial functions, as well as in the neuroinflammatory pathways involved in diseases of the central nervous system. IL-6 levels in the brain are low under normal physiological conditions. A dramatic increase in its expression and secretion has been reported during various neurological disorders (9). IL-6 also indirectly induces angiogenesis by stimulating

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vascular endothelial growth factor (VEGF) expression. Angiogenesis is an essential component of inflammation and its resolution (10). TNF-α is a critical cytokine involved in initiating inflammatory responses. It also plays a central role in oxidative stress generation and the apoptosis of endothelial cells, which are widely observed in SAH (11).

The current treatments for vasospasm include hypervolemia, hypertension, hemodilution therapy, balloon angioplasty, and pharmacological therapy, such as calcium channel antagonists (12,13). Therefore, alternative vasospasm treatments with better effects are needed. Tocilizumab (TCZ) is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G1k subclass that acts against soluble and membrane-bound IL-6 receptors (IL-6R) (14). It has been reported to be safe and effective after chimeric antigen receptor T-cell therapy, rheumatoid arthritis, and giant cell arteritis (15). TCZ inhibits the binding of IL-6 to its receptors and thus reduces its proinflammatory activity by competing with both the soluble and membrane-bound forms of human IL-6R.

This study explored the effects of IL-6R antagonist TCZ on morphological changes, endothelial apoptosis, and biochemically measured cytokines in the post-SAH rat brain and basilar artery tissues. The study also investigated the possible neuroprotective properties of TCZ.

MATERIAL AND METHOD

Animals

A total of 48 (animal study) Wistar albino female rats weighing approximately 300–350 g were used (KONÜDAM Experimental Animal Research Center, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey; 15/03/2019). In this study, in order to protect animal rights in their work, the principles of the Guide for the Care and Use of Laboratory Animals were accordanced. They were raised under standard laboratory conditions, fed a standard diet, and supplied with water ad libitum. The animals were housed in air-conditioned rooms at a temperature of 20°C±2°C, 50%±5% humidity, 15 times/hour (100% clean air) ventilation, and a 12/12 h light–dark cycle.

Experimental Groups

The animals were initially randomized into four groups (one control and three experimental groups), each of which consisted of 12 rats. The rats were randomly assigned to one of the following: (1) normal control (without SAH); (2) SAH (without treatment); (3) SAH treated with saline (SAH + SAL); and (4) SAH treated with TCZ (SAH + TCZ). The control group did not undergo any intervention. The rats in the second group underwent experimental SAH without treatment and were sacrificed 72 h after SAH. The rats in the third group were administered three doses of intraperitoneal saline (0.2 mL) every 24 h, with the first dose administered immediately after SAH was induced. The rats were then sacrificed 72 h after SAH. The rats in the fourth group were administered with three doses of intraperitoneal TCZ (8 mg/kg) every 24 h, with the first dose given immediately after the SAH was induced. The animals were sacrificed at 72 h after SAH induction. Mean arterial blood pressure and blood gas levels were monitored through a catheter inserted into the femoral artery.

Surgical Procedures

All surgical procedures were performed under sterile conditions. No surgical intervention was performed on the first group of rats, whereas in the experimental groups, experimental SAH was performed. The animals were pre-anesthetized with the subcutaneous administration of ketamine (35 mg/kg; Ketalar, Eczacıbaşı İlaç ve Ticaret A.Ş., İstanbul, Türkiye) and xylazine (5 mg/kg; Rompun; Bayer Türk Kimya San. Ltd., Şti. İstanbul, Türkiye). Subsequently, 0.1 mL of non-heparinized blood was collected from the tail arteries. With the application of aseptic techniques, a midline nuchal incision was made. The dermal and subdermal tissues, fascia, and paravertebral muscles were dissected to expose the atlantooccipital membrane. Next, the atlantooccipital membrane was dissected, and a 25-gauge needle was inserted through the dura mater and the arachnoid membrane into the cisterna magna. After the cisterna magna was punctured, 0.1 mL cerebrospinal fluid (CSF) was withdrawn. An equal amount of autologous arterial blood was then slowly injected into the cisterna magna within 2 min. Immediately after the procedure, the muscle tissue and skin were sutured, and the surgical area was closed. The rats were maintained in the 45° Trendelenburg position for 15 min to permit the pooling of blood around the basilar artery and throughout the brain (16).

Biochemical Procedures

The arterial tissues were homogenized (10% w/v) separately in ice-cold 50-mM potassium phosphate buffer (pH 7.4). The homogenate was centrifuged at 10,000 g for 20 min at 4°C, and the supernatant was used for different assays. Caspase 3, signal transducer and activator of transcription 3 (STAT-3), IL-6, IL-1, TNF-α, Bcl-2–associated X-protein (BAX), and VEGF were measured using commercially available enzyme-linked immunosorbent assay kits, according to the manufacturer's instructions.

Immunohistopathological Assessment

After all animals were anesthetized, the brains were removed, fixed in 10% formaldehyde for 2 days, and then subjected to histopathological examination at the XXX University Histology and Embryology Department. A series of basilar artery sections were obtained and divided into several subgroups for hematoxylin and eosin (H&E) staining, immunohistochemistry, and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining.

H&E staining: Paraffin-embedded samples of the brain and artery tissues were deparaffinized and rehydrated in decreasing alcohol concentrations. The sections were stained in hematoxylin for 2 min and in eosin for 1 min, dehydrated, and covered with a coverslip. The luminal area of the basilar arteries was calculated from the perimeter of the luminal border, and the area contained within the boundaries of the internal elastic lamina was disregarded. The thickness of the wall between the lumen and the external border of the muscle layer was measured at four quadrants of each section of the basilar artery (17).

TUNEL staining: The brain and artery sections were stained using a TUNEL staining kit according to the manufacturer's protocol for the in situ apoptosis detection kit (Merck Millipore, Darmstadt, Germany). TUNEL-positive cells were identified using fluorescein-dUTP with 3,3′ -diaminobenzidine. The apoptotic index was calculated as the percentage of immunoreactive nuclei per total number of endothelial cells (17).

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 for Windows (IBM Inc., Chicago, IL, USA). Data were expressed as mean±standard deviation for numerical variables and frequency (percentage) for categorical variables. The Kruskal–Wallis test was used to compare the study groups, and its own post-hoc test was used to analyze significant results. A $p < 0.05$ was considered statistically significant.

RESULTS

A total of 48 animals were included in the study. All animals survived and completed the study without any mortality.

Biochemical Findings

The serum levels of all biochemical measurements varied significantly between the study groups (**Table 1**). The serum STAT-3 level was significantly lower in the control than in the other groups ($p = 0.002$). Among the treatment groups, the SAH + TOC group showed a significantly lower serum STAT-3 level than those in the SAH and SAH + SAL groups. The serum caspase-3 level was significantly higher in the control than in the other groups ($p = 0.029$). The serum BAX level was highest in the SAH group and lowest in the SAH + TOC group ($p = 0.016$). The IL-6 and IL-1β levels were significantly lowest in the SAH + TOC group ($p = 0.002$ and $p = 0.015$, respectively). The TNF-α level was significantly lower in the control group but higher in the SAH + SAL group ($p = 0.001$). The VEGF level was significantly lower in the SAH + TOC group but higher in the SAH and SAH + SAL groups ($p < 0.001$).

Immunohistopathological Assessment

The mean cross-sectional area of the basilar artery decreased more significantly in the SAH group than those in the control and SAH + SAL groups (**Figures 1** and **2**). The SAH + TCZ had a significantly bigger basilar artery lumen compared with the SAH and SAH + SAL groups ($p = 0.001$). SAH significantly increased the thickness of the basilar arterial wall, which was reversed by TCZ treatment ($p = 0.001$). SAH significantly increased the apoptotic index in the endothelium, but TCZ treatment significantly reduced the percentage of apoptotic endothelial cells ($p = 0.001$; **Table 2**).

Table 1. Measurements of biochemical parameters

	STAT-3 (pg/mL)	Caspase-3 (pg/mL)	BAX (pg/mL)	IL-6 (pg/mL)	IL-1β (pg/mL)	TNF-α (pg/mL)	VEGF (pg/mL)
Control	10.25±0.50	1.99±0.13	4.91±0.32	421.36±75.92	422.46±75.23	59.14±12.59	48.41±1.92
SAH	11.14±0.57	1.91±0.10	5.03±0.42	443.07±62.044	453.07±62.04	67.13±19.50	54.98±2.91
SAH + SAL	11.30±0.48	1.85±0.94	4.96±0.32	446.07±114.32	463.56±83.75	69.19±21.02	53.56±4.91
SAH + TOC	10.93±0.38	1.81±0.11	4.56±0.33	355.07±89.69	438.05±110.77	61.93±16.94	43.40±5.49
p	0.002*	0.029*	0.016*	0.002*	0.015*	0.001*	<0,001*
Post-hoc	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4

* $p < 0.05$, Kruskal–Wallis test. 1, control group; 2, SAH group; 3, SAH + SAL group; 4 SAH + TOC group: Study groups, vs: versus denoting the significant ($p < 0.05$) pairwise comparisons. STAT-3: signal transducer and activator of transcription 3; BAX: BCL-2 associated X-protein; IL-6: interleukin-6; IL-1β: interleukin 1 beta; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor; SAH: subarachnoid hemorrhage; SAH + SAL: SAH treated with saline; SAH + TOC: SAH treated with tocilizumab.

Table 2. Immunohistopathological measurements

	Apoptotic index	Wall thickness (μ)	Lumen of the basilar artery (μm²)
Control	2.50±0.26	29.69±0.72	13232.98±412.01
SAH	27.6±1.48	37.32±0.77	9718.06±245.09
SAH + SAL	25.8±1.74	39.87±0.51	9837.46±179.16
SAH + TOC	8.10±0.56	31.92±0.69	11848.36±311.33
p	0.001*	0.001*	0.001*
Post-hoc	1 vs 2 1 vs 3 1 vs 4 2 vs 4 3 vs 4	1 vs 2 1 vs 3 3 vs 4	1 vs 2 1 vs 3 1 vs 4 2 vs 4

*p < 0.05, Kruskal–Wallis test. 1, control group; 2, SAH group; 3, SAH + SAL group; 4 SAH + TOC group: Study groups, vs: versus denoting the significant (p < 0.05) pairwise comparisons. STAT-3: signal transducer and activator of transcription 3; BAX: BCL-2 associated X-protein; IL-6: interleukin-6; IL-1: interleukin 1 beta; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor; SAH: subarachnoid hemorrhage; SAH + SAL: SAH treated with saline; SAH + TOC: SAH treated with tocilizumab.

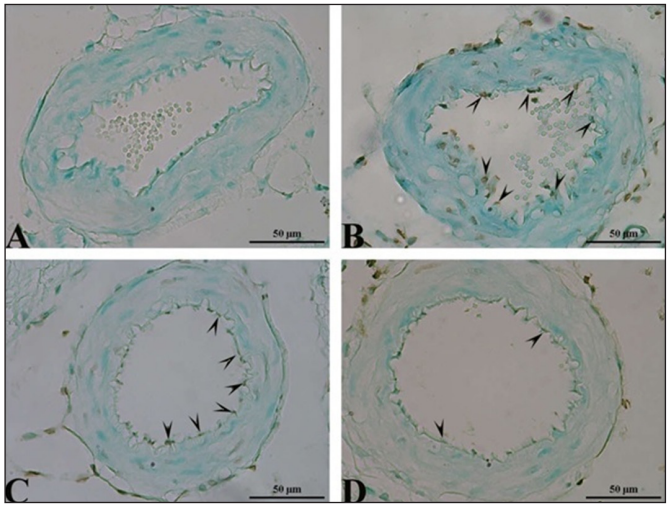

Figure 1. Terminal deoxynucleotidyl transferase dUTP nick end labeling staining of the basilar artery figures of four study groups. A: Control group; B: subarachnoid hemorrhage (SAH) group; C: SAH treated with saline (SAH + SAL) group; D: SAH treated with tocilizumab (SAH + TOC) group.

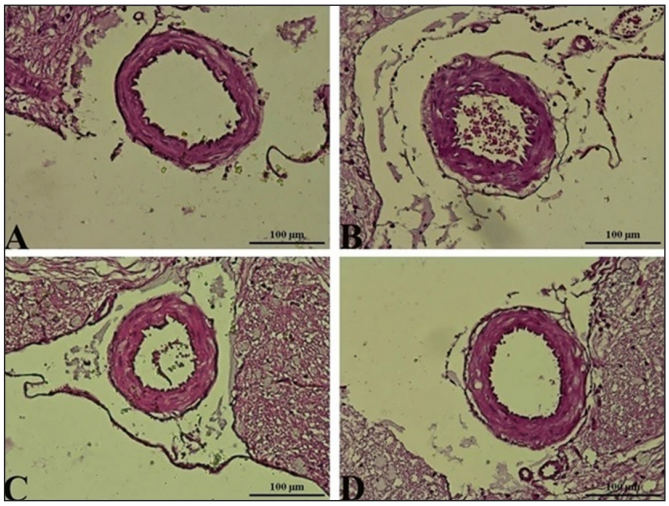

Figure 2. Hematoxylin and eosin staining of the basilar artery figures of four study groups. A: Control group; B: Subarachnoid hemorrhage (SAH) group; C: SAH treated with saline (SAH + SAL) group; D: SAH treated with tocilizumab (SAH + TOC) group.

DISCUSSION

In this study, the IL-6 level was significantly higher in the SAH group than that in the control group, suggesting that the inflammatory responses mediated by IL-6 play an important role in SAH progression.

Previous studies have demonstrated that IL-6 levels are elevated in the CSF following SAH, indicating that higher IL-6 levels in CSF are correlated with worse clinical outcomes (8). Graetz et al. (18) confirmed that, in all patients with SAH, proinflammatory IL-6 activation was observed, with the highest levels in CSF, followed by the brain parenchyma and plasma, which also showed significantly increased values. TCZ can block IL-6 signaling by competing for both soluble and membrane-bound forms of IL-6R (19). Previous studies have successfully proven the efficacy of TCZ against immune diseases characterized by IL-6 inflammation (20,21). Thus, TCZ could lower IL-6 levels to mitigate the effects of SAH.

IL-6 production can be upregulated by various stimuli, including IL-1, TNF-α, and transforming growth factor beta. The proinflammatory cytokine IL-1 is a key mediator of neuronal injury after acute brain injury (22). Previous studies have demonstrated that increased IL-1 levels activate an inflammatory response after SAH (23). Greenhalgh et al. (24) confirmed that IL-1 is involved in cellular injury after brain insult and inhibits IL-1, with IL-1 receptor antagonist reducing the measures of brain injury after in vivo SAH. In this study, the IL-6 level was increased in the SAH group compared to the controls, while TCZ lowered the IL-6 levels.

TNF-α has also been correlated with delayed complications in SAH such as delayed cerebral ischemia (25). Our findings indicate that the TNF-α levels were higher in the SAH group than in the control group, suggesting that elevated TNF-α levels in CSF may be associated with SAH progression. Previous studies have confirmed that both IL-6 and TNF-α levels in CSF are associated with SAH and that they may be directly involved in SAH development and progression (26).

In the present study, TCZ significantly improved angiographic and histologic vasospasm by attenuating the apoptosis of endothelial cells and proliferation of smooth muscle cells. Zhou et al. (27) demonstrated that histologic vasospasm is accompanied by endothelial damage caused by apoptosis and that the signaling pathways for apoptosis after SAH in endothelial cells were mediated, at least partially, by TNF receptor 1, which in turn recruited caspase-8, which then activated caspase-3. A recent study showed that TCZ reduces vasospasms, demonstrating potential as a treatment for vasospasms and apoptosis in neuronal cells induced by SAH (28). Smooth muscle proliferation promotes vasospasm and is characterized by intimal thickening and wall stiffness (29). Several apoptotic pathways may be activated in SAH, including the death receptor pathway, p53, the caspase-dependent and -independent pathways, and the mitochondrial pathway (30). SAH thus functions as an external stress event, which, through a mechanism that is not yet fully understood, can initiate cellular apoptosis (31). In the present study, all apoptosis components measured were increased by SAH.

VEGF is a crucial factor of angiogenesis that stimulates vascular permeability under physiological and pathological conditions (32). A study reported that VEGF expression was induced in the brain after experimental SAH because of increased blood–brain barrier permeability (33,34). Previous studies have shown that VEGF levels increased in animals to which experimental SAH was performed. Nishimoto et al. (35) found that serum VEGF levels markedly decreased with TCZ therapy for active rheumatoid arthritis. Similarly, in the present study, TCZ decreased VEGF expression in the post-SAH rat model. The normalization of VEGF by blocking the IL-6 function alone indicates that IL-6 is essential for VEGF expression.

This study has some limitations. One is the lack of the measurement of IL-6 and other cytokine levels in the plasma and CSF. This study is also limited by the absence of blood biochemical and immunohistochemical evaluations of IL-6, IL-1, TNF-α, and VEGF levels.

CONCLUSION

This study demonstrated that TCZ, a marketed drug commonly used for immune-mediated diseases, is safe and effective for treating experimental SAH. Further, our findings reveal experimental evidence of the potential clinical application of TCZ in SAH and suggest further investigation of TCZ as a clinically accepted pharmacologic treatment option.

Abbreviation

BAX: Bcl-2 associated X-protein, CSF: Cerebrospinal Fluid, H&E: Hematoxylin and Eosin, IL: Interleukin, SAH: Subarachnoid Hemorrhage, SPSS: Statistical Package of Social Science, STAT: Signal Transducer and Activator of Transcription, TCZ: Tocilizumab, TNF-alpha: Tumor Necrosis Factor-Alpha, TUNEL: Labeling, VEGF: Vascular Endothelial Growth Factor

ETHICAL DECLARATIONS

Ethics Committee Approval: The animal handling protocol was approved by the Institutional Experimental Animal Research Unit Committee of the Necmettin Erbakan University (Date: 26.02.2016, Decision No: 2016-001).

Informed Consent: No informed consent is required in this experimental animal study.

Referee Evaluation Process: Externally peer reviewed.

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