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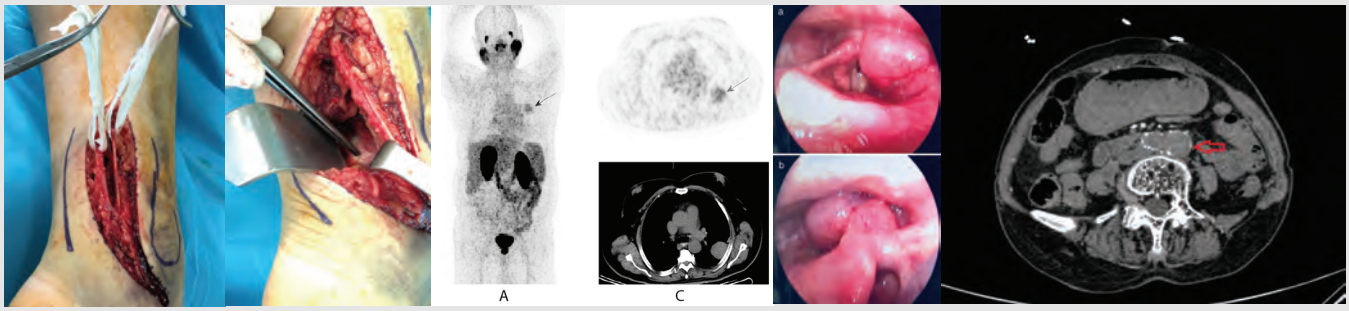

Highlights

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables.

Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text).

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
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Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

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Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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CONTENTS

ORIGINAL ARTICLE

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The Effect of Maternal Obesity on Perinatal and Neonatal Outcomes

Miraç Özalp, Veli Mihmanlı

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Abstract

Objective: To investigate the relationship between maternal obesity and perinatal and neonatal outcomes in primigravid pregnant women.

Methods: A total of 162 primigravid pregnant women were categorized into four groups based on their body mass index (BMI), age, gravida (number of pregnancies), parity (number of births), gestational week, pre-pregnancy body weight, height, prenatal final body weight, delivery patterns and indications, pre-eclampsia, fetuses small for gestational age (SGA), hemoglobin values at the time of hospitalization and after 24 h of delivery, transfusional requirements, birth weight of the babies, neonatal intensive care need, and the babies' 1^{st}-5^{th} min APGAR scores were compared among the groups.

Results: No significant differences were noted among the BMI groups in terms of age, gestational age, delivery type, neonatal intensive care unit needs, and transfusional requirements. The weights of the babies, weight gain during the pregnancy, incidence of pre-eclampsia, incidence of SGA, and APGAR scores were found to be statistically significantly different among the groups.

Conclusion: The findings of the present study indicate that maternal obesity is an important factor for increasing risk of pregnancy complications and neonatal morbidity.

Keywords: Obesity, maternal outcomes, perinatal outcomes, pre-eclampsia, small for gestational age

INTRODUCTION

Obesity is a disease characterized by increased body fat tissues (1). It is a common health problem across the world, with increasing incidence reported among women of the reproductive age (1). Obesity was initially accepted as a problem of the developed countries, but its prevalence has gradually spread across the world, irrespective of the east-west or rich-poor situation, in parallel with the increasing income levels in the developing countries with the adoption of the western lifestyle, increased energy intake, decreased energy expenditure, and, finally, the rural-to-urban immigration phenomena (2). With reference to the definition of obesity by the World Health Organization (WHO) in 1995 and 2000 and as updated in 2004, it can be classified in the context of body mass index (BMI). BMI is a simple measure used to define a person as underweight, normal-weight, overweight, or obese by using the relationship between weight and length in adult individuals. BMI is calculated by dividing the body weight in kilograms into the square of the length in meters (expressed in kg/m^2) (1).

Pregnancy is marked by a period of rapid body weight changes, and uncontrolled increases or decreases in weight during this period could result in critical health concerns for the mother as well as the fetus (3). Recommendations for weight gain during pregnancy aim at the best outcome of pregnancy in terms of mother and baby (3,4). In 2009, the American Institute of Medicine (IOM) published a recommendation guide to regulate the weight gain based on different BMI levels in pregnancy, in accordance with the WHO's classification of obesity (5). Pregnant

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obese women face risks such as gestational diabetes, hypertensive diseases, thromboembolism, preterm labor, macrosomia, birth complications, and increased rate of cesarean (C/S) delivery (5).

This study aimed to investigate the relationship between maternal obesity and perinatal and neonatal outcomes among primigravid pregnant women.

METHODS

The present study is a prospective observational study on 162 primigravid pregnant women admitted to the Emergency Delivery Room of Okmeydanı Training and Research Hospital between 01.01.2015 and 30.04.2015. The research was approved by the Ethics Committee of Okmeydanı Training and Research Hospital (23.12.2014; no: 256). The information on pregnancy age, gravida (number of pregnancies), parity (number of births), gestational week, pre-pregnancy body weight, length, BMI, prenatal final body weight, delivery patterns and indications, incidence of pre-eclampsia, and fetuses who were small for gestational age (SGA) according to the gestational week, hemoglobin (Hb) values at the time of hospitalization and after 24 h of delivery, transfusional requirements, birth weight (BW) of babies, neonatal intensive care need, and the babies' 1st-5th min APGAR scores were obtained from the subjects' medical files. The subjects were accordingly categorized into 4 different BMI groups that were then compared for different parameters. The underweight group had BMI <18.5 kg/m^2, the normal group had BMI: 18.5-24.9 kg/m^2, the overweight group had BMI: 25-29.9 kg/m^2, and the obese group had BMI >30 kg/m^2. SGA refers to a child born with BW and/or birth length under two standard deviations for the gestational age and sex of the population. All pregnant women who wished to participate in the study were informed about the research goals, and their written informed consents were obtained. Pregnant women with pre-pregnancy chronic internal or surgical diseases or with multiple pregnancies and who happened to have fetuses with an anomaly detected during the screening were excluded from the study, and the remaining primigravid pregnant women were included.

Statistical Analysis

The number cruncher statistical system (NCSS) 2007 software (Kaysville, Utah, USA) was used for statistical analysis. When evaluating the study data, One-Way analysis of variance was used to compare among three or more groups with normal distribution in comparison with quantitative data and Tukey's honestly significant difference test for the determination of the group causing differences used alongside descriptive statistical methods (such as mean, standard deviation, median, frequency, ratio, minimum, and maximum). The Kruskal-Wallis test was applied for the comparison of 3 or more groups with no normal distribution, while the Mann-Whitney U test was used for the determination of the group causing the difference. Pearson's chi-square test and Fisher-Freeman-Halton Exact test were used for comparison of the qualitative data. Significance was evaluated at $p<0.01$ and $p<0.05$.

RESULTS

The ages of the pregnant women included in the study ranged from 18 to 42 years, with the mean value of 27.15±5.03 years. Examination of the weight of the pregnant women revealed a range of 43-107 kg (mean: 65.16±11.76 kg), while the height of the pregnant women was 145-180 cm (mean: 161.72±7.69 cm), and the BMI values were 16.81-43.97 kg/m^2 (mean: 25.20±5.56 kg/m^2) (Table 1).

The gestational period of the subjects ranged from 28 to 42.71 weeks (mean duration: 38.46±2.26 weeks). The weight of their babies ranged from 1.185 to 4.800 g (average: 3212.59±672.28 g) (Table 2).

The gain in the weight of the pregnant women ranged between 3 and 22 kg (mean gain value: 10.78±2.80 kg). In terms of the birth type, normal spontaneous birth (NSB) was recorded for 46.9% (n=76), while cesarean (C/S) birth was recorded for 53.1% (n=86) of the subjects.

No significant difference was noted among the BMI groups in terms of age, gestational age, delivery type, neonatal intensive care unit (ICU) needs, and transfusional requirements (Table 3).

Among the BMI groups, it was observed that the weights of the babies of obese pregnant women were significantly higher than those of underweight, normal-weight, and overweight pregnant women (p=0.003; p=0.046; p=0.049, respectively).

Among the BMI groups, the weight gain among the underweight pregnant women were found to be significantly greater than that among the overweight and obese pregnant women (p=0.001; p=0.001, respectively).

Table 1. Findings related to the maternal characteristics

	Minimum-maximum	Mean ± SD
Age (years)	18-42	27.15±5.03
Weight (kg)	43-107	65.16±11.76
Length (cm)	145-180	161.72±7.69
Body mass index (kg/m^2)	16.81-43.97	25.20±5.56

SD: Standard deviation

The evaluation of the incidence of pre-eclampsia revealed statistically significantly lower incidence in the underweight pregnant women than in the overweight and obese pregnant women (p=0.008; p=0.030, respectively).

Examination of the BMI groups revealed that the rate of SGA incidence in babies of underweight pregnant women was significantly greater than that of obese pregnant women (p=0.006).

Finally, on comparison of the APGAR scores, 1st-min APGAR scores of babies of the normal group and the 5th-min APGAR scores of the babies of the underweight group were significantly greater than those of the overweight and obese groups (p=0.045, p=0.025).

DISCUSSION

Dramatic differences have been recorded in the recommendations made to the women about body weight gain during pregnancy when compared to that 60 years ago. Past studies have shown that body weight gain in pregnancy is related to maternal characteristics such as BMI at the onset of pregnancy, age, parity, education level, the ethnic group as well as the sociodemographic characteristics (6-8). In a study conducted by Marshall et al. (9) on 64,272 pregnant women, 82.5% of the subjects were found to be obese according to their BMI and 15.6% of them belonged to the morbidly obese group and 1.8% to the super obese group. In our study, 162 pregnant women were examined prospectively, and the mean body weight of these women before their pregnancies was found to be 65.16±11.76 kg, the mean height was 161.72±7.69 cm, and the mean BMI at the onset of pregnancy was 25.20±5.56 kg/m^2. When the cases were divided into 4 baseline BMI groups, 23.2% (n=37) of the pregnant women were recorded as underweight, 25.9% (n=42) as normal-weight, 26.5% (n=43) as overweight, and 24.6% (n=40) as obese. However, this study was a single-centered study conducted on a small population, which limits consideration of its inference to diverse populations.

As per the IOM-2009 recommendation, the body weight gain should be in the range of 12.6-18.1 kg for the underweight, 11.3-15.9 kg for the normal-weight, 6.8-11.3 kg for the overweight, and 5.0-9.1 kg for the obese pregnant women (5). A study by DeVader et al. (10) reported 94,696 pregnant women with a normal BMI, of which 60% of the pregnant women did not have a recommended body weight gain, 17.2% of the body weight was less than the recommended value by IOM, and 42.8% of the body weight was higher than the recommended value. In this study, however, it was found that subjects in the underweight group gained 12.65 kg, those in normal group gained 11.37 kg, those in the overweight group gained 10.10 kg, and those in the obese group gained 9.19 kg; these increases in the weight gain were consistent with the IOM recommendations. We noted that the gained weights of the pregnant women in the underweight and

Table 2. Evaluation of variables among the BMI groups

Mean ± SD		Underweight (n=37)	Normal (n=42)	Overweight (n=43)	Obese (n=40)	[a]p
		Mean ± SD	Mean ± SD	Mean ± SD		
Weeks of pregnancy		38.61±1.64	38.32±1.68	38.16±3.10	38.78±2.25	0.606
Birth weight (g)		3005.95±514.50	3149.62±511.16	3158.49±791.12	3528.00±722.97	0.004**
Weight gain during pregnancy (kg)		12.65±2.43	11.37±2.17	10.10±2.80	9.19±2.58	<0.001**
		n (%)	n (%)	n (%)	n (%)	
Birth type	NSD	22 (59.5)	19 (45.2)	20 (46.5)	14 (35.0)	[c]0.199
	C/S	15 (40.5)	23 (54.8)	23 (53.5)	26 (65.0)	

[a]One-way analysis of variance, [c]Pearson's chi-square test, *p<0.05, **p<0.01, SD: Standard deviation, BMI: Body mass index

Table 3. Evaluation of variables among the BMI groups

	Underweight (n=37)	Normal (n=42)	Overweight (n=43)	Obese (n=40)	p
	n (%)	n (%)	n (%)	n (%)	
Pre-eclampsia	1 (2.7)	6 (14.3)	10 (23.3)	8 (20.0)	[d]0.040*
Small for gestational age	9 (24.3)	6 (14.3)	5 (11.6)	1 (2.5)	[d]0.033*
Blood transfusion	4 (10.8)	5 (11.9)	7 (16.3)	5 (12.5)	[d]0.915
Neonatal intensive care need	10 (27.0)	4 (9.5)	12 (27.9)	11 (27.5)	[c]0.126

[c]Pearson's chi-square test, [d]Fisher-Freeman-Halton Exact test, *p<0.05, **p<0.01, BMI: Body mass index

normal-weight groups were statistically significantly higher than those in the overweight and obese groups (p=0.001; p=0.001, respectively).

Another criterion investigated in the study was the relationship between the maternal BMI and newborn weights. In the Baeten's series, infant birth rates of >4000 g were 10.7% in 50,378 cases with normal BMI, 14.5% in 17547 cases with high BMI, and 17.3% in 9.806 cases with very high BMI; the macrosomic infant birth rate in obese pregnant women was found to be significantly higher (11). The results of this study indicate that the mean birth weight of babies was 3005.95 g in the underweight BMI group, 3149.62 g in the normal-weight group, 3158.49 g in the overweight group, and 3528.00 g in the obese group. Statistically significant difference was noted among the groups in terms of the weight of newborns (p=0.004). The comparison of the birth weeks among the 4 groups based on the BMI revealed that the mean birth weeks were 38.6, 38.3, 38.1, and 38.7 for the normal, overweight, and obese groups, respectively. No statistically significant difference was noted among the BMI groups in terms of the gestational weeks (p>0.05). In a study conducted by Vinturache et al. (12) in Canada in 2015 on 3.388 pregnant women, the mean birth weeks of 62.5% of the subjects in the normal-weight group were found to be $39^{0/7}$-$40^{6/7}$ weeks (accepted as "term"), those in the subjects in the overweight group were $41^{0/7}$-$41^{6/7}$ weeks ("late period"), and those of subjects in the obese group were $37^{0/7}$-$38^{6/7}$ ("early period"). In this study, the smaller sample size was deemed attributable for these differences.

The NSB rate was found to be 46.9% (n=76) and the C/S delivery rate 53.1% (n=86) in all cases. The NSB rate for all groups were 59.5%, 45.2%, 46.5%, and 35% for the underweight, normal, overweight, and obese groups, respectively. In addition, the C/S delivery rates were 40.5%, 54.8%, 53.5%, and 65% in the underweight, normal-weight, overweight, and obese groups, respectively. In this study, no statistically significant difference was recorded between the birth types based on the BMI groups. When we examined the study with the large database of Baeten et al. (11), we noted that the C/S delivery rate was 16.6% among 50,425 pregnant women with normal BMI, 23.2% among 17,571 pregnant women with high BMI, and 32% among 9.817 pregnant women with very high BMI. The reasons for the lack of a statistically significant result in this series can be attributed to the small number of patients involved and that the study hospital was a tertiary center.

When the results obtained were examined in terms of pregnancy-related cases of hypertension and pre-eclampsia, the respective risk ratio were found to be 2.7% in underweight, 14.3% in normal-weight, 23.3% in overweight, and 20% in obese patients. It should be emphasized that this risk increase was not only seen in obese women with very high BMI (≥30) but also in overweight women with BMI 25-29.9. In the study of Kılık et al. (13) in 2019, no significant difference was noted in the BMI between a pre-eclampsia group (30.6±5.6 kg/m^2) and the control group (31.0±4.2 kg/m^2). But this past study includes a very small study population. In another study by Young et al. (14) conducted in 2016, the incidence of hypertensive disease in pregnancy was 7.2% and that of pre-eclampsia was 0.09% in a group of subjects with BMI <30, while the corresponding ratios were 14.5% and 0.22% in the group with BMI >30, respectively. Kumari (15) reported pregnancy-related hypertension rates of 28.7% in 188 obese patients, while this rate was 3% in the control group (BMI 20-25); the difference herein was statistically significant. The results of these past studies are in line with the present findings supporting that pregnancy-related hypertension is an important risk factor both in overweight and obese pregnant women. Thus, it is extremely important that hypertensive diseases be included among the most important causes of maternal mortality. Another fetal-neonatal variable examined in our study was the SGA development rates. The SGA incidence rates were revealed to be 24.3% for the underweight group, 14.3% for the normal-weight group, 11.6% for the overweight group, and 2.5% for the obese group; statistically significant differences were recorded among the BMI groups in terms of the SGA incidence in newborns (p=0.033). In the 2001 series of Sebire et al. (16), the SGA infant birth rates were found to be 5.45% in the normal BMI group and 4.58% and 4.76% in the groups with high and very high BMI, respectively. Examination of the results of studies on this subject revealed that the findings obtained in our series were consistent with those of the literature.

In our study, the postoperative 1st- and 5th-min APGAR scores were evaluated for 4 BMI groups as another fetal-neonatal criterion. These 4 groups were compared in terms of low APGAR scores. The mean 1st-min and 5th APGAR scores were 7.27 and 8.78 in the underweight group, 7.69 and 8.74 in the normal-weight group, 6.83 and 8.00 in the overweight group, and 6.78 and 8.33 in the obese group, respectively. There was a statistically significant difference among the BMI groups in terms of both the 1st-min APGAR scores (p=0.045) and the 5th-min APGAR scores (p=0.025). When we examined the study of Bianco et al. (17) published in 1998, we noted that the ratio of babies with APGAR score <7 at the 5th min was 0.7% in 613 morbidly obese pregnant women and 0.4% in 11,313 control pregnant women. Although the author did not detect any statistically significant

difference, the birthrate of newborns with low APGAR scores was higher in the morbidly obese group. The results of these past studies were found to be consistent with those obtained in our series. The incidence of low APGAR score was found to be higher in children born from obese pregnant women than in those born from normal-weight pregnant women.

The last fetal-neonatal parameter evaluated was to examine the follow-up rates of infants in the neonatal ICUs among all 4 BMI groups. The need for neonatal ICU after birth was 10% in the underweight group, 9.5% in the normal-weight group, 11.6% in the overweight group, and 12.7% in the obese group. No statistically significant difference was noted among the 4 groups. Because the incidences of pregnancy complications were higher in the overweight and obese pregnant women, their newborns showed more frequent cases of transient tachypnea and respiratory distress, and the rate of neonatal follow-up in the premature ward was higher, with the number of hypoglycemic newborns being higher due to the higher rate of gestational diabetes and the larger size of the baby at birth. SGA emerged as the leading newborn ICU requirement of babies of pregnant women in the underweight group.

In our study, Hb values at the time of admission and that at the 24th h after birth as well as the blood transfusional requirements of the subjects were also examined. The mean Hb value at admission was 11.99 and the mean postpartum Hb was 10.28 in the underweight group, while it was 11.58 and 9.94 in the normal group, 12.15 and 10.33 in the overweight group, and 12.53 and 10.97 in the obese group, respectively. Statistically significant difference was noted among the BMI groups in terms of admission Hb values (p=0.023). In addition, statistically significant difference was noted among the BMI groups in terms of the Hb values at the 24th hour after birth (p=0.032). The blood transfusion rates were found to be 10.8% in the underweight group, 11.9% in the normal group, 16.3% in the overweight group, and 12.5% in the obese group, albeit there was no statistical significance among them.

CONCLUSION

The findings of the present study suggest that obesity is an important factor that contributes to increasing pregnancy complications and fetal-neonatal morbidity. Therefore, starting a pregnancy with an appropriate BMI is expected to minimize the risk of complications among the mothers and newborn. Moreover, it will also help realize the principles of a healthy mother and a healthy newborn, which are the main objectives of an obstetric intervention.

Ethics

Ethics Committee Approval: Ethics Committee of Okmeydanı Training and Research Hospital (23.12.2014; no: 256).

Informed Consent: All pregnant women who wished to participate in the study were informed about the research goals, and their written informed consents were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Ö., V.M., Design: M.Ö., V.M., Data Collection or Processing: M.Ö., Analysis or Interpretation: M.Ö., V.M., Literature Search: M.Ö., Writing: M.Ö.

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

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ORIGINAL ARTICLE

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Fixation of Posterior Malleolus is Enough for Syndesmotic Stability: Fact or Fiction?

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Abstract

Objective: This study aimed to evaluate syndesmotic stability following anatomic reduction and fixation of the posterior malleolus (PM) of ankle fractures with syndesmotic instability, without utilizing a classical syndesmotic screw.

Methods: We have retrospectively evaluated patients with PM fracture and syndesmotic displacement between September 2012 and May 2017. The inclusion criteria were as follows: patients with (1) PM fracture, either isolated or a part of bi-/trimalleolar fracture with syndesmotic instability; (2) fractures fixed through a posterior approach; (3) fractures fixed with either screw or plate-screw combination; and (4) Bartonicek type 2-5 fractures. Among 145 patients, 41 (27 female, 14 male) met the inclusion criteria. The average age was 42.65 years, and the mean follow-up time was 19.41 months. Ankle fractures were classified according to the Weber classification, while PM fractures according to the Bartonicek classification. Perioperative reduction was evaluated by anteroposterior, lateral, and mortise views. Perioperative and postoperative stability was evaluated using Cotton and fibular translation tests. Postoperative syndemotic reduction was evaluated with computed tomography (CT) scan according to Dikos and Futamura.

Results: According to the Weber classification, 22 were type B, 17 type C, and 2 unclassified because they did not get lateral malleolus fracture. According to Bartonicek classification, 17 fractures (41.5%) were type 2, 14 (34.1%) type 3, 9 (22%) type 4, and 1 (2.4%) type 5. All patients had unilateral fractures. On postoperative CT scan evaluation, 38 (92.68%) patients got syndesmotic reduction, and 3 (7.32%) got syndesmotic malreduction.

Conclusion: This study demonstrated that if appropriate surgical principles are followed, and meticulous attention paid for reduction and fixation, fixing only the PM achieves syndesmotic stability for patients with PM fracture and syndesmotic diastasis. The indication for PM fixation should not be based on size alone. Not all, but PM fractures with syndesmotic displacement should be operated.

Keywords: Posterior malleolus, syndesmosis, fixation

INTRODUCTION

Ankle fractures are common injuries (1). Posterior malleolus (PM) fractures are present in 10% to 44% of all ankle fractures (2). The presence of a posterior fragment is well-established to have a negative effect on the clinical outcome of ankle fractures (3).

Classically, for posterior fragments >25%-33% of the anteroposterior diameter of the articular surface of the distal tibia as measured on a plain lateral radiograph, open reduction and internal fixation of the fragment should be performed (4,5). However, plain radiography poorly assesses the trimalleolar ankle fractures (6). But in the last decade, the indication for surgery of PM has been changed. Syndesmotic stability, the involvement of the fibular notch, and the presence of intercalary fragments are more important than the size of the fracture and the amount of the fractured articular surface (7).

The syndesmosis represents a complex ligamentous structure formed by four ligaments: anterior inferior tibiofibular ligament (AITFL), interosseous ligament (IOL), posterior inferior

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tibiofibular ligament (PITFL), and inferior transverse ligament (8). Among them, PITFL forms the main resistance against diastasis with 42%, followed by AITFL with 35% and IOL with 22% (9). Biomechanical studies suggest the restoration of the posterior aspect of the tibiofibular ligament with the fixation of the PM, obviating the need for syndesmotic stabilization (9,10). A cadaveric study showed that PITFL remained attached to the PM fragment in cases of PM fracture (10).

A preoperative computed tomography (CT) scan is imperative to evaluate the fragment size, comminution, articular impaction, and syndesmotic disruption (11). With the frequent use of the CT scan to assess the 3D geometry of PM fractures, an increasing number of authors recommend internal fixation of any displaced PM involving the fibular notch regardless of its size because it recreates the notch for fibular reduction and substantially contributes to syndesmotic stability (7).

This study aimed to evaluate syndesmotic integrity following anatomic reduction and fixation of the PM of ankle fractures with syndesmotic instability, without utilizing a classical syndesmotic screw. Our hypothesis was that fixing only the PM would result in distal tibiofibular reduction on postoperative CT scans and stability on clinical tests.

METHODS

We have retrospectively evaluated patients with PM fracture and syndesmotic instability between September 2012 and May 2017. The inclusion criteria were as follows: patients with (1) PM fracture, either isolated or a part of bi-/trimalleolar fracture with syndesmotic instability; (2) fractures fixed through a posterior approach; (3) fractures fixed with either screw or plate-screw combination; and (4) Bartonicek type 2-5 fractures. The exclusion criteria, on the other hand, were as follows: patients (1) with pathologic fractures, (2) with posterior pilon fractures (3) with less than 1-year follow-up, (4) without preoperative or postoperative CT scans, (5) with fractures fixed anteriorly, (6) with a laterally placed syndesmotic screw, and (7) with Bartonicek type 1 fractures.

The study was approved by the institutional review board of Bakırköy Training and Research Hospital (2017-18-30).

Informed consent was taken from all patients.

All patients who have been included in the study were evaluated preoperatively and postoperatively using X-rays (anteroposterior, lateral, and mortise views) and CT scans. Preoperative syndesmotic stability was evaluated by mortise views and Cotton and fibular translation tests. Syndesmotic reduction was evaluated according to Dikos et al. (12), with three measurements chosen to contain three deforming vectors (13). Tibiofibular clear space was measured as the interval between medial fibula and the tip of the posterior tibial tubercle, which reflects mediolateral diastasis. Anterior tibiofibular interval is measured as the distance between the anterior tibia and the anterior fibula to reflect anteroposterior deviation of the fibula. Finally, θ fib is measured for the rotational malalignment of the fibula, which is the angle formed between a tangential line to the anterior and posterior tibial tubercles and a line through the anterior and posterior fibular tubercles. All measurements were done using transverse CT scans 1 cm proximal from the ankle joint level and bilaterally, to use the noninjured side as a control group for the calculation of the difference between the injured and noninjured sides (Figure 1, Table 1).

Ankle fractures were classified according to the Weber classification. Infrasyndesmotic lateral malleolus fractures were classified as type A, syndesmotic fractures as type B, and supra syndesmotic fractures as type C. But this system is not sufficient, because it does not include PM. Therefore, fractures were additionally classified according to Bartonicek classification: extraincisural fragments were classified as type 1, posterolateral fragments as type 2, posteromedial two-part fragments as type 3, large posterolateral triangular fragments as type 4, and irregular osteoporotic fractures as type 5 (7).

All patients underwent operation on the prone position under either general or spinal anesthesia. A thigh tourniquet was used to prevent bleeding. A modified posterolateral approach was used to access PM and, if necessary, lateral malleolus (Figure 2). Standard posterolateral approach gives a nice view of the PM fragment and maintains a window for anatomical reduction and rigid fixation (14). A modification was used to avoid excessive force during ecartation. The sural nerve and lesser saphenous vein were protected during superficial dissection (Figure 3). The PM was reached between the flexor hallucis longus and peroneus longus interval, which were reduced and fixed in the first place. Care was taken to prevent posterior-inferior tibiofibular ligament displacement (Figure 4), followed by, from the same approach, the reduction and lateral fixation of lateral malleolus fracture using the advantage of a modified approach. The medial

Table 1. Normal side-to-side differences

	Mean variability	Maximum variability
TFCS (mm)	0.7±0.6 (0.0-2.7)	1.9
ATF (mm)	0.8±0.7 (0.0-3.0)	2.3
θ fib (°)	2.9±1.8 (0.2-6.4)	6.5

TFCS: Tibiofibular clear space, ATF: Anterior tibiofibular interval

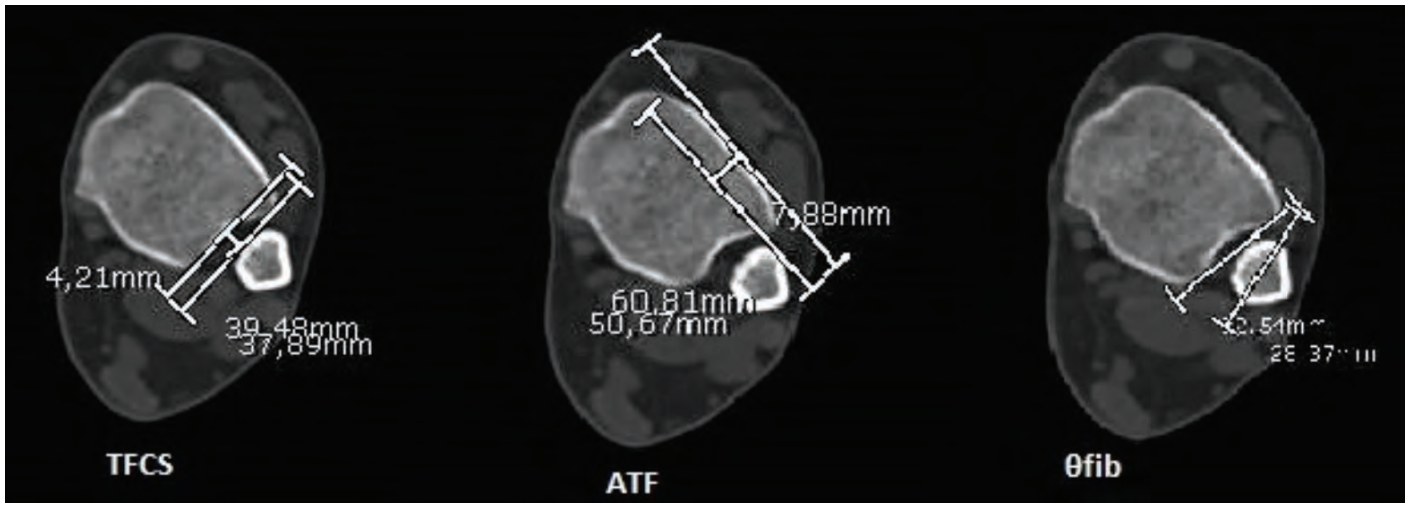

Figure 1. Measurements according to Dikos
TFCS: Tibiofibular clear space, ATF: Anterior tibiofibular interval

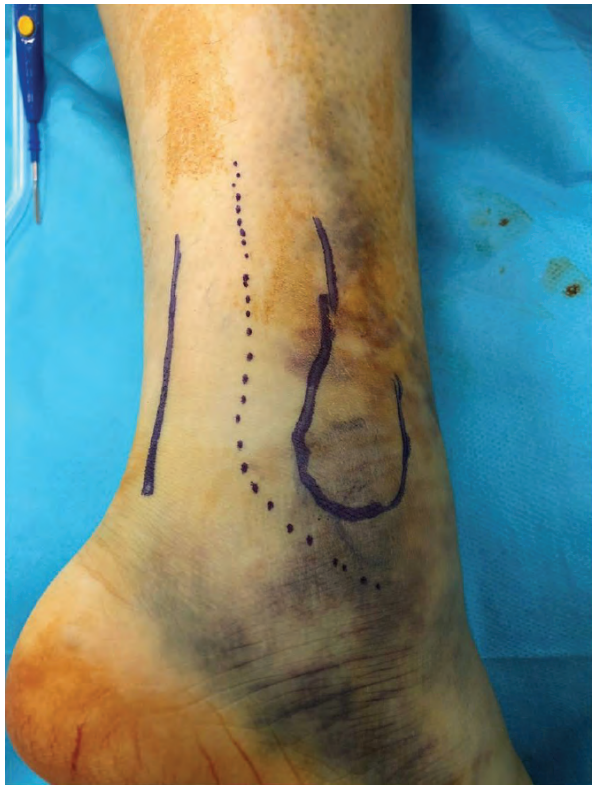

Figure 2. Modified posterolateral approach. The straight line shows the lateral border of the Achilles tendon. The lateral fibula is marked. Between these lines, the dotted line with a curve on the tip of the lateral malleolus shows a modified approach

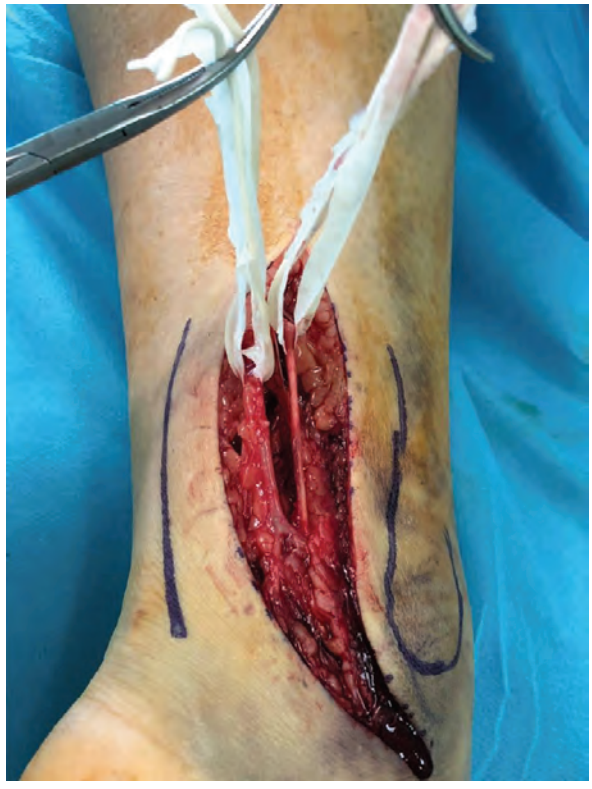

Figure 3. Sural nerve and lesser saphenous nerve

malleolus fracture treatment used a separate medial curve incision. All reductions and fixations were controlled using the intraoperative C-arm; the anteroposterior, lateral, and mortise views were obtained for this purpose. Intraoperatively, after the fixation of all fractures, the fibular translation and Cotton tests evaluated the syndesmotic integrity. With the Cotton test, medial and lateral forces are applied to the talus with the ankle in the neutral position. The fibula translation test examines the fibula in the anteroposterior direction, which is positive when an excessive amount of translation is felt compared to the opposite ankle (15).

Postoperative X-rays and CT scans were taken to evaluate the quality of fracture and syndesmosis reduction that was measured according to Dikos et al. (12) and Futamura et al. (13).

Postoperatively, all fractures were stabilized for 6 weeks with a short leg splint. Regular clinic assessments were made at 2 weeks, 6 weeks, 10 weeks, 14 weeks, 6 months, and 12 months, with radiologic assessments on every clinical control except for the second week. CT scans were taken in the early postoperative period and in the final follow-up visit. After 6 weeks, progressive weight-bearing was started according to the healing status shown in clinic X-ray follow-ups.

Cotton and fibular translation tests evaluated the postoperative syndesmotic stability.

Each patient and their related radiological imaging were evaluated individually, with their result noted as a percentage value. No other statistical measurement was used.

RESULTS

Among 145 patients, 41 met the inclusion criteria. Among the excluded 101 patients, 85 were conservatively treated, 1 got a pathologic fracture, 2 were fixed anteriorly, 6 got an additional syndesmotic screw, and 10 had a <1-year follow-up period.

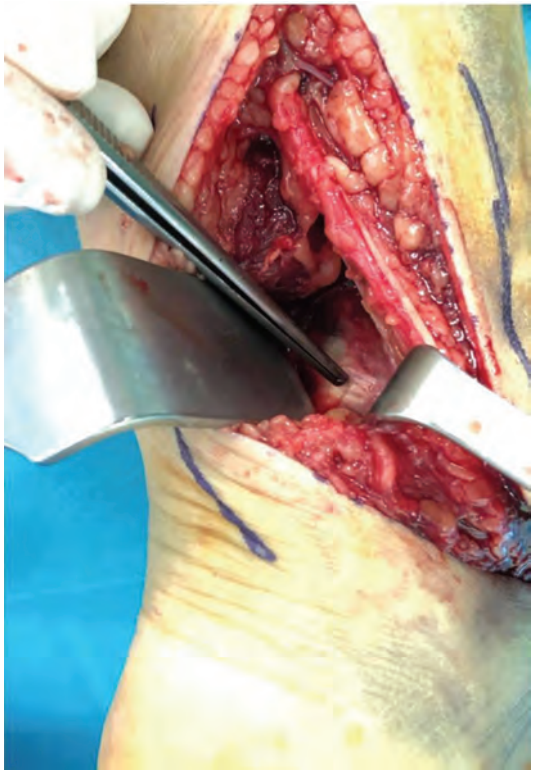

Figure 4. PITFL on the tip of forceps
PITFL: Posterior inferior tibiofibular ligament

Also, 27 were female and 14 male, with an average age of 42.65 (range, 15-75) years. All patients had unilateral fractures, with 24 on the right side and 17 on the left side. The mean follow-up time was 19.41 (range, 12-67) months.

According to the Weber classification, 22 were type B, 17 type C, and 2 unclassified because they did not get lateral malleolus fracture.

According to Bartonicek classification, 17 fractures (41.5%) were type 2, 14 (34.1%) type 3, 9 (22%) type 4, and 1 (2.4%) type 5.

On postoperative CT scan evaluation, 38 (92.68%) patients got and maintained the syndesmotic reduction upon the final follow-up visit. Three (7.32%) patients got syndesmotic malreduction. After patient evaluation, one got malreduced syndesmosis because of the malreduced PM (Figure 5). One patient got ankle arthrosis because of complicated aberrant heterotopic ossification, causing syndesmotic diastasis, which can be interpreted as a complication rather than an early malreduction (Figure 6). The last one had a fixation problem, and the screw used to fix PM penetrated the tibiofibular space, avoiding syndesmotic reduction (Figure 7). According to Bartonicek classification, these three were distributed one by one to types 2-4.

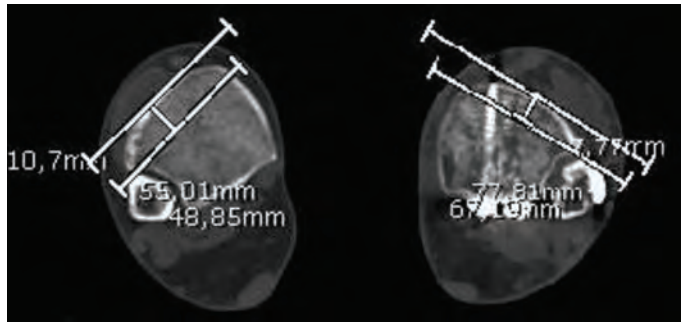

Figure 5. Malreduced syndesmosis secondary to malreduced PM
PM: Posterior malleolus

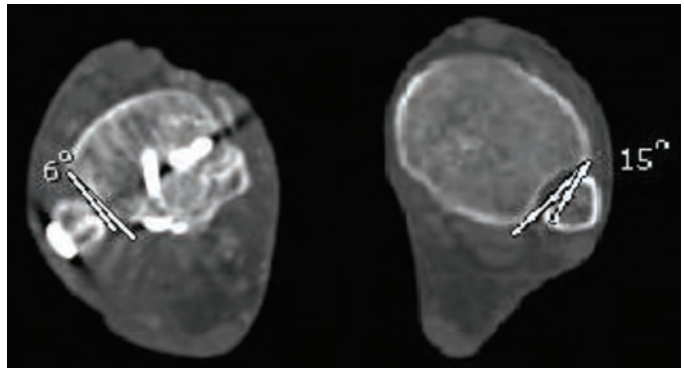

Figure 6. Malreduced syndesmosis secondary to arthrosis

The three malreduced patients were unstable when clinically evaluated by the Cotton and fibular translation tests postoperatively.

No major intraoperative complications were noted. Three patients developed a superficial infection, which was managed using local dressing and antibiotics. Nonunions or implant failure was not seen as well.

DISCUSSION

This study demonstrated that if appropriate surgical principles are followed, and meticulous attention paid for reduction and fixation, fixing only the PM achieves syndesmotic reduction, as well as stability for patients with PM fracture and syndesmotic diastasis, and diminishes the need for an extra syndesmotic screw. Our surgical principles for PM fractures with syndesmotic displacement are as follows: prone positioning, distally curved modified posterolateral incision to avoid excessive force during ecartation, starting fixation from PM and then moving to lateral and medial malleoli if exists, perioperative Cotton and fibular translation tests for stability, and AP, lateral, and mortise views for reduction evaluation. In this study, syndesmotic reduction was achieved 92.68% (38/41) of the time, and two of the three malreduced syndesmoses could be avoided.

In the past, the indication for PM surgery was a fragment size >25% to 33% of the articular surface and displacement >2 mm (4,5). But over the last decades, these indications have evolved. Studies suggest that the involvement of the fibular notch, impacted intercalary articular fragments, and syndesmotic instability has greater therapeutic relevance than the size of the fragment and amount of the fractured articular surface (7). Moreover, plain X-rays have been shown to be insufficient in evaluating the nature of the fracture and syndesmotic stability (6). Therefore in this study, we used pre- and postoperative CT scans in evaluating the fracture pattern and syndesmotic stability. For indication, we take care of the recent evolutions.

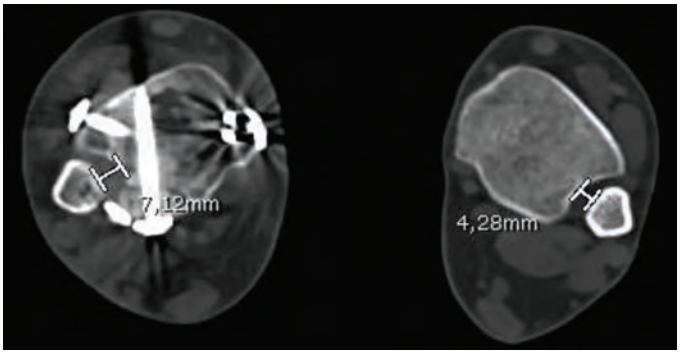

Figure 7. Malreduced syndesmosis secondary to malfixation

The size was not taken care because even the mere presence of a small posterior fragment causes a negative effect on ankle fracture outcomes (3). In this study, all patients with fibular notch, syndesmotic instability, and impacted intercalary articular fragment involvement underwent operation.

According to the Weber classification, 22 were type B, 17 type C, and 2 unclassified because the first one was an isolated PM fracture with syndesmotic displacement and the second were medial and PM fractures with syndesmotic displacement. The number of type B fractures may be confusing, but Tornetta has shown an incidence of 39% syndesmotic instability with type B fractures (16).

According to Bartonicek classification, 17 fractures (41.5%) were type 2, 14 (34.1%) type 3, 9 (22%) type 4, and 1 (2.4%) type 5, which are different from the study of Bartonicek et al. (7), possibly because of the patient group we evaluated. In this study, only surgically treated patients were included. Therefore, there are no Bartonicek type 1 fractures.

All the operations were made in the prone position, and fixation started from the PM. In their comparative series, Miller et al. (17) compared supine and prone positioning for the operation, concluding that 24.5% of the patients in the supine position needed an extra posterior fixation and the rate of syndesmotic instability was reduced when prone positioning and direct fixation of the PM were first performed. Also, fixing the PM in the first step reduces the distal fibula to the exact length through the PITFL (1).

Indirect reduction using ligamentotaxis and fixation from anterior to posterior can be used for PM fractures. But direct reduction and fixation from the posterior side have been shown to provide better reduction quality and functional outcomes (18,19). Also, it is more stable than the anteroposterior fixation (14,15).

Perioperative and postoperative syndesmotic stability control was achieved by using fibular translation and Cotton tests, which were chosen for this study because they were two of the three tests advised by the ESSKA-AFAS consensus panel (20). At the time of surgery, all patients showed syndesmotic stability. But on the postoperative CT scan evaluation, 3 patients got syndesmotic malreduction, and 38 achieved stability. This rate of stability is consistent with the literature (17). Of the three malreduced patients, two could be avoided. One of them got a screw in the tibiofibular space, causing syndesmotic diastasis. The other one was a PM malreduction, causing syndesmotic malreduction. They were cases operated at the beginning of the learning curve.

Perioperative X-ray examination must be much more precise to prevent these complications, and the tests should be done bilaterally.

Three (7.32%) patients got syndesmotic malreduction. According to Bartonicek classification, these three were distributed one by one to types 2-4. The number of malreduction is the same for all the types. But when looking at the percentages of malreduction, type 4 has 11%; type 3, 7%; and type 2, 5.8%. The incidence rises with the type, probably because the energy amount rises with the type of the fracture (7).

In their study, Miller et al. (17) evaluated the effect of PM fixation on syndesmotic integrity. But the current study differs from Miller et al. (17) in important ways. First and foremost, they have decided prone or supine positioning preoperatively according to the percentage of PM and used 25% as a fixation indication for PM. They also did not use a preoperative CT scan for surgical decision-making. Secondly, in Miller et al. (17) study, they did not give the sequence for the surgery. We operated patients following the posterior, lateral, and medial malleolus sequences.

According to Gardner et al. (10), the fixation of PM alone gives 70% syndesmotic stability. In our study, all appropriately fixed PM gave enough syndesmotic stability according to perioperative stress testing and postoperative CT scans.

Another advantage of fixing only PM for syndesmotic integrity is negating any additional screw or tightrope for the stabilization of syndesmosis. Also, it diminishes the need for screw removal, and postoperative rehabilitation can be quicker (1).

Study Limitations

Our study has some weaknesses and limitations: the retrospective design of the study, no follow-up with questionnaires, and small sample size.

CONCLUSION

This study shows that for the fixation of PM, instead of articular involvement, the size of the fragment and displacement, the involvement of the fibular notch, impacted intercalary articular fragments, and syndesmotic instability should be used. We suggest that not all PM fractures but those with syndesmotic displacement should be approached surgically. Second, the fixation of PM without an additional syndesmotic screw is stable enough.

Ethics

Ethics Committee Approval: The study was approved by the institutional review board of Bakırköy Training and Research Hospital (2017-18-30).

Informed Consent: Informed consent was taken from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.B., N.Z., Concept: E.B., Design: E.B., Data Collection or Processing: N.Z., Analysis or Interpretation: N.Z., Literature Search: E.B., N.Z., Writing: E.B., N.Z.

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

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ORIGINAL ARTICLE

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PSMA-positive Secondary Tumors in ^{68}Ga-PSMA PET/CT Imaging in Patients with Prostate Cancer

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Abstract

Objective: The objective of this research was to examine the prostate-specific membrane antigen (PSMA)-positive secondary tumor incidence in ^{68}Ga-PSMA positron emission tomography/computed tomography (PET/CT) imaging in patients with prostate cancer (PCa).

Methods: Data from 605 ^{68}Ga-PSMA PET/CT images of 506 PCa patients used for staging or restaging were analyzed retrospectively. Further, documented separately, PSMA-positive lesions were found not to be PCa-related and were then suspected as secondary tumors. The results were analyzed from those lesions that were histopathologically verified.

Results: Nine patients (1.8%) had a PSMA-positive lesion that was believed to be a secondary tumor. Of these lesions, five (1%) were histopathologically confirmed, and secondary tumors were diagnosed (namely, squamous cell non-small cell lung cancer, papillary thyroid cancer (TCa) lymph node metastasis, minimally invasive TCa, colon cancer and liver metastases, and fibrohistiocytic tumor). The mean serum PSA value for patients diagnosed with secondary tumor was 29.42 (0.01-142.22) ng/mL. For PSMA-positive secondary tumor lesions, the mean maximum standard unit value was 9.74 (3.9-15).

Conclusion: Especially in the presence of atypical location and insufficient serum PSA values, PSMA-positive lesions should be considered secondary tumors, and differential diagnostic studies should be conducted.

Keywords: ^{68}Ga-PSMA PET/CT, PSMA uptake, secondary tumor

INTRODUCTION

Prostate-specific membrane antigen (PSMA), also referred to as folate hydrolase I or glutamate carboxypeptidase II, is expressed at elevated levels in prostatic adenocarcinoma prostate cancer (PCa) cells 100-1000 times that of normal prostate tissue (1,2). Moreover, PSMA expression may increase with high tumor grade/stage and also with tumor dedifferentiation, metastatic disease, and hormone resistance (1,2). This is the target site for ^{68}Ga-labeled agents that bind and cause the agent to be internalized, thereby allowing detection on positron emission tomography (PET) imaging. Compared to traditional imaging, ^{68}Ga-PSMA PET/computed tomography (CT) has superior diagnostic capabilities to detect tumoral focus in primary staging and biochemical recurrence (BCR) of patients with PCa (3-5).

^{68}Ga-PSMA uptake can usually be seen in the salivary glands, nasopharynx, vocal cords, thyroid gland, duodenum, small intestines, spleen, liver, pancreas, stomach, adrenal gland, kidneys, rectum, testes, and varying degrees of vertebral bone marrow (6,7). In addition, PSMA expression was demonstrated in a number of nonprostatic malignant and non-malignant conditions found in ^{68}Ga-PSMA PET/CT (8-10) and was also seen in neovascular capillary endothelium in the peritumoral areas of a variety of epithelial malignancies (2). This condition resulted in the discovery of incidental non-prostatic tumors on ^{68}Ga-PSMA PET/CT imaging performed for both primary staging and BCR and led to its use for diagnostic purposes for malignancies such as hepatocellular Ca and renal Ca. In this study, the incidence of PSMA-positive secondary tumors found in ^{68}Ga-PSMA PET/CT

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imaging were examined and histopathologic findings of these tumors were evaluated.

METHODS

Patients

Retrospectively, the medical history and imaging data of PCa patients who underwent ^{68}Ga-PSMA-PET/CT at our nuclear medicine department from July 2017 to December 2019 were analyzed. The PSMA-positive lesions believed to be secondary tumors of these patients were examined for imaging and histopathologic findings. Patients with secondary malignancy prior to ^{68}Ga-PSMA-PET/CT imaging were excluded from the study. If lesions were found, localization, CT findings, and clinical findings were evaluated together, and pathologies with no association with PCa and high likelihood of being benign were not included.

All patients signed written informed consent forms for the purpose of reviewing and publishing their results. Hence, this study was accepted by the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (01.07.2020/14).

Imaging and Analysis

Patients were imaged using an integrated PET/CT scanner consisting of a full-ring HI-REZ LSO PET and a six-slice CT scanner (Siemens Biograph 6, Chicago, IL, USA). Each patient was given a standardized weight-based dose of 2 MBq/kg (range 70-180 MBq) ^{68}Ga-PSMA. Further, PET/CT scan was performed at 60 min post-injection with an emission time of 3 min per bed position from the vertex to the upper thigh. Prior to emission imaging, low-dose CT for attenuation correction and anatomic localization was performed with the following parameters: 50 mA, 140 kV, and 5 mm section thickness. Image analysis was carried out on the Esoft multimodality computer platform (Siemens Medical Solutions, Erlangen, Germany). The images were then interpreted by an experienced nuclear medicine physician on the basis of a visual examination with knowledge of the patient's clinical history and the findings of previous imaging studies. A positive scan was characterized as such when the PSMA uptake was visually above the background and did not correspond to the physiologic distribution sites. The maximum standardized uptake values (SUV_{max}) of each lesion were determined by the region of interest applied in the transaxial attenuation-corrected PET slice with the highest uptake.

Patients were suspected of developing PSMA-positive secondary tumor in the presence of one of the following criteria:

- A lesion with increased PSMA uptake was detected at a site that was unexpected on the basis of the PCa metastasis pattern.

- Inconsistency between PSMA-positive lesion, patient clinical progression, and serum PSA values was found.

Any site of incidental PSMA uptake found not to be PCa-related and suspected of being a secondary tumor was documented separately. PSMA-positive lesions suspected of secondary tumors were verified by histopathologic evaluation whenever possible.

Statistical Analysis

During the evaluation of the study data, descriptive statistical methods such as mean, median, frequency, ratio, minimum, and maximum value were used.

RESULTS

Retrospectively, data from 605 ^{68}Ga-PSMA PET/CT images performed for staging or restaging of 506 PCa patients were reevaluated. Nine (1.8%) of these patients were reported as having PSMA-positive lesion suspected of being a secondary tumor. The mean age of patients was 67.4 years (52-79) with six patients having ^{68}Ga-PSMA PET/CT imaging for restaging and three patients having it for staging purposes. Of these lesions, five (1%) were histopathologically confirmed and had the following secondary tumor diagnoses (Table 1): squamous cell non-small cell lung cancer (NSCLC) presenting as mass lesion in the left lung (Figure 1), papillary thyroid cancer (TCa) presenting as lymph node in the right cervical region, minimally invasive TCa as a nodular lesion in the right lobe of the thyroid, metastatic colon cancer presenting as multiple hypodense lesions in the liver and lesion in the descending colon, and fibrohistiocytic tumor presenting as subcutaneous

Table 1. General characteristics of histopathologically verified PSMA-positive secondary tumor

PSMA-positive lesion	PSA	SUV_{max}	Histopathological diagnosis
Mass lesion at left lung	4.65	7.84	Squamous cell lung cancer
Nodular lesion at right thyroid lobe	0.01	15	Minimally invasive thyroid cancer
Lymph node at right cervical chain	0.01	8.09	Papillary thyroid cancer lymph node metastasis
Descending colon lesion to multiple liver lesion	142.2	13.86	Colon cancer to liver metastases
Subcutaneous lesion at dorsal region	0.2	3.9	Fibrohistiocytic tumor

PSMA: Prostate-specific membrane antigen, PSA: Prostate-specific antigen, SUV_{max}: Maximum standardized uptake values

lesion in the dorsal region. Of these patients, the mean serum PSA value was 29.42 (0.01-142.22) ng/mL. Cases with PSMA-positive secondary tumor diagnosis had a mean SUV_{max} value of 9.74 (3.9-15). In the case with histopathologic diagnosis of fibrohistiocytic tumor, the SUV_{max} lesion value was lower than the physiologic SUV_{max} values for the liver and higher than the other cases. With histopathologic investigation, three patients with a diagnosis of malignancy were treated, while two cases with biopsy were included in the treatment program for medical oncology. In three patients with increased PSMA expression in the thyroid gland (SUV_{max} values 3.54, 5.55, and 2.27), no advanced research could be conducted due to the clinical condition of the patients or follow-up in an outpatient center. A patient with PSMA-positive lesion (SUV_{max} 25.13) in the spleen parenchyma had a diagnosis of hemangioma with magnetic resonance imaging.

DISCUSSION

While prostate-specific, PSMA is not specific for PCa. PSMA-positive incidental secondary tumor lesions have been observed since the first application of ^{68}Ga-PSMA PET/CT imaging to PCa patients. PSMA is expressed in various forms of tumor neovasculature, such as renal cell carcinomas, bladder carcinomas, colonic adenocarcinomas, gastric cancers, TCa, gliomas, LC, malignant melanomas, osteosarcomas, and soft tissue tumors, but not normal tissue vasculature (11-17). There are several publications in the literature on incidental secondary malignancies found on ^{68}Ga-PSMA PET/CT imaging performed for the purpose of staging or restaging patients with PCa (18,19). Hepatocellular carcinoma, renal adenocarcinoma, follicular and papillary TCa, follicular lymphoma, multiple myeloma, gastrointestinal stromal tumor, rectal adenocarcinoma, colon adenocarcinoma, penile squamous cell carcinoma (SCC), primary LC, breast cancer, urothelial cancer, and oropharynx SCC (20-33) were included in these articles.

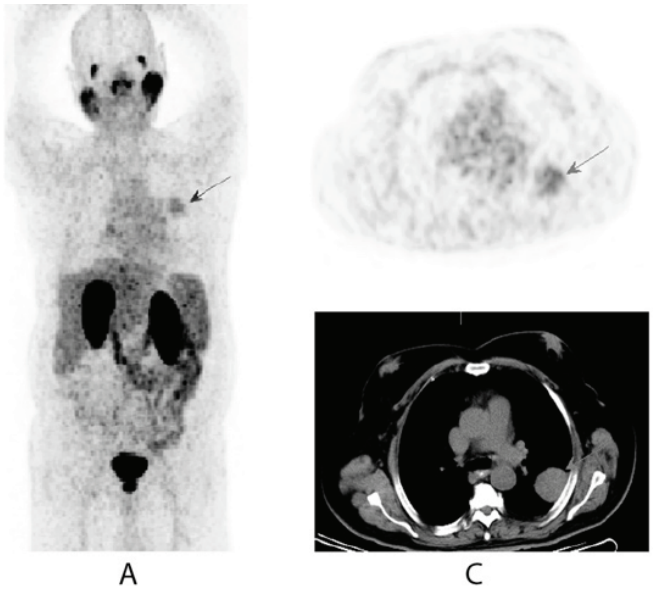

Figure 1. A 73-year-old PCa patient is imaged with ^{68}Ga PSMA PET/CT for restaging. The serum PSA value was 4.65 ng/mL. PSMA expressing lung mass was found in the left lung (SUV_{max}: 7.84) on ^{68}Ga PSMA PET/CT imaging (arrow). Histopathological evaluation revealed squamous cell NSCLC

PCa: Prostate cancer, PSMA: Prostate-specific membrane antigen, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standardized uptake values, NSCLC: Non-small cell lung cancer

In this 506-patient cohort group, 1.8% of patients were reported as having PSMA-positive incidental lesions which were suspected as a secondary tumor. Of these lesions, five (1%) were histopathologically verified, and secondary tumor diagnosis was made (papillary TCa, minimally invasive TCa, NSCLC, colon cancer, and fibrohistiocytic tumor). Osman et al. (34) observed synchronous primary malignancy in 5 patients in a 764 PCa case series of PET/CT imaging performed (0.7%, 2 lung adenocarcinoma, 1 diffuse B-cell lymphoma, 1 PCa, and 1 SCC of the base of the tongue).

In this study, TCa was the most frequently identified secondary incidental tumor. A diagnosis of metastatic papillary TCa was made in one patient with histopathologic examination of lymph nodes in the cervical region. This patient had a papillary TCa focus of 0.5 cm identified with thyroidectomy pathology. Pathologic involvement of the thyroid gland was not present on ^{68}Ga-PSMA PET/CT imaging. It was concluded that the small size of the primary lesion was effective due to the lack of detection of PSMA-positive lesion in the thyroid gland. One patient had minimally invasive follicular TCa diagnostic sites with thyroidectomy pathology of PSMA-positive thyroid lesion. Immunohistochemistry studies of TCa cases showed that neovascular PSMA expression was more common in TCa relative to benign thyroid pathologies and that there were high levels of PSMA expression in poorly or undifferentiated and aggressive TCa (13,34). This property resulted in the use of ^{68}Ga-PSMA PET/CT imaging and potential radionuclide treatment for metastasis identification in high thyroglobulin and radioiodine-negative TCa, in particular (35).

One of our cases diagnosed with an incidental PSMA-positive secondary tumor had squamous cell NSCLC. In the literature, both squamous and adenocarcinoma NSCLC cases have been reported to be identified with ^{68}Ga-PSMA PET/CT imaging (28,36,37). Schmidt et al. (11) immunohistochemistry studies on NSLC cases found neovascular PSMA expression in 49% of NSCLC

and tumor cell PSMA expression in 6%. High neovascular PSMA expression was also reported to be associated with higher tumor grading.

In this study, a patient with PSMA-positive colon cancer in the descending colon also demonstrated PSMA expression in liver metastases. Cases of PSMA-positive colorectal cancer have been documented in the literature, and immunohistochemistry studies have reported that higher-grade colorectal tumors appear to have higher PSMA expression and higher risk of distant metastases and vascular invasion. However, there was no statistical difference in overall survival or disease-free survival based on PSMA expression (16,27,28).

In analysis, the mean serum PSA value for five patients with histopathologic verification of secondary tumor diagnosis was 29.42 (0.01-142.22) ng/mL. There were two patients with 0.01 ng/mL and one patient with 0.2 ng/mL, whereas three patients had low serum PSA value with PSMA-positive lesion identified. When lesions are evaluated with anatomic localization, the low serum PSA value should be assessed as a factor warning of the presence of pathology outside the prostate.

Study Limitations

The most significant limitation of this retrospectively designed study is that all incidental PSMA-positive lesions found on ^{68}Ga PSMA PET/CT imaging were not histopathologically verified. Another drawback is that differential diagnosis of synchronous secondary malignancies could not be made because advanced diagnostic studies could not be conducted in patients with extensive visceral metastases due to the clinical status and ethical reasons.

CONCLUSION

PCa patients may rarely have PSMA-positive secondary tumors found in ^{68}Ga PSMA PET/CT images. In particular, considering the CT properties of the atypical PCa metastasis location and the presence of PSMA-positive lesions that do not respond to patient clinical symptoms, consideration should be given to the possibility of secondary tumors and differential diagnostic studies be performed.

Ethics

Ethics Committee Approval: Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (01.07.2020/14).

Informed Consent: All patients signed written informed consent forms for the purpose of reviewing and publishing their results.

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

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The Relationship Between Nursing Students' Attitudes Toward the Nursing Profession Concerning Career Choice and Motivation

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Abstract

Objective: Nursing students must voluntarily choose the nursing profession and be motivated to have a positive attitude toward the profession. The study aimed to evaluate the relationship between nursing students' attitudes toward their profession and their career choice and motivations.

Methods: The study included 302 nursing students studying at a state university in Turkey between December 2018 and January 2019. The data were collected using the data collection form, attitude scale for nursing profession, the scale of nurse career choice, motivation sources, and problems scale. Descriptive statistics, independent t-test, Mann-Whitney U test, One-Way analysis of variance test, Kruskal-Wallis test, and Pearson's and Spearman's correlation coefficients were used for data analysis.

Results: The mean age of the participants was 21.1±1.6 years, and 87.4% of them were women. A statistically significant difference was found among the class levels and attitudes toward the nursing profession, properties of nursing profession, prefer for nursing profession, nurse career choice, occupational compliance, vital causes, and negative motivation ($p<0.05$). A statistically significant difference was found between gender and attitudes toward the nursing profession, properties of nursing profession, prefer for nursing profession, general position of nursing profession, occupational compliance, motivation, intrinsic motivation, extrinsic motivation, and negative motivation ($p<0.05$). A statistically significant positive correlation was found between attitudes toward the nursing profession and the following factors: nurse career choice, occupational compliance, motivation, intrinsic motivation, extrinsic motivation, and negative motivation ($p<0.05$).

Conclusion: According to this study, it was concluded that nurse career choice and motivation positively affected nursing students' attitudes toward the nursing profession.

Keywords: Attitude, career choice, motivation, nursing, nursing student

INTRODUCTION

Nursing remains a common career choice for both younger and older students entering university. The choice of the nursing profession may be related to internal factors (such as liking the profession, having a partner in the healthcare field, being kept apprised of the nursing profession, and having the desire to help others or a general affection for people) or external factors (such as job guarantee, family desires or pressure, and exam scores) (1). One study in regional Australia found that the main reasons students enrolled into nursing programs were altruism, vocation, and interest, and they consider nursing to be a career that one can easily progress up the promotion ladder (2).

The motivation for students' choosing nursing is related to both internal and external factors including being admitted to the first choice program, choosing a field according to personal interests, opening opportunities for career progression, making a

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career in nursing, having nursing/caring experience, and having a desire to help others (3). In a study by Jirwe and Rudman (3), approximately 75% of the respondents wanted to care for and help others. Problems of the nursing profession such as educational differences, financial situations, traditional values and culture, gender differences, work environment, and media's depiction of nurses have negative effects on the motivations of nursing students. Existing literature demonstrates a poor perception of nurses from the public through media misperception (4,5). Participants in the study by Liu expressed that they would not encourage their children, especially their sons, to become nurses according to traditional norms and values (5).

The attitudes of professionals working within a given field are important to achieving professional status and providing qualified service to the society. The attitude of the individual toward a profession affects his or her success and satisfaction within the profession (5). To make an accurate and appropriate career choice decision, the person should know what he or she wants, know what he or she can do, and have positive attitudes toward that profession. A study by Al Jarrah (6) revealed that nursing students' attitudes toward the profession are positive. A study by Čukljek et al. (7) also found that nursing students had positive attitudes toward nursing in their first and third years of study, and a positive change in attitudes was influenced by the acquisition of knowledge and skills.

Although there are a limited number of studies examining the attitudes of nursing students regarding the profession and factors that lead them to select the profession, no study has evaluated the relationship between the attitudes toward the profession, factors of profession selection, and sources of motivation using valid and reliable scales (8,9). Thus, this study aimed to determine the relationship between nursing students' attitudes toward the nursing profession concerning career choice and motivation.

METHODS

Study Design

This study was a descriptive, cross-sectional study.

Settings and Participants

The study population included 474 nursing students from a state university between December 2018 and January 2019 in Ankara, Turkey (class I: 174, class II: 168, and class IV: 132 students). There was no sample exclusion process, and the total population was invited to participate. Of the nursing students, only 302 met the following inclusion criteria: being a nursing student and willing to participate in the study. Class III was excluded in the study because there were no students enrolled. Nursing students were not admitted to Gülhane Nursing Faculty in the academic year September 2016 because of the July 15, 2016, coup attempt in Turkey. Thus, there were only first-, second-, and fourth-year nursing students at the beginning of the study in 2018.

Data Collection Tools

Data Collection Form: The data collection form was created by the researchers after completing the literature review. The form consisted of 10 questions about demographic data, reasons for choosing the profession, attitudes toward the profession, and future planning related to the profession.

Attitude Scale for Nursing Profession (ASNP): The scale was developed in 2010 by Coban and Kasikci (10) to evaluate attitudes toward the nursing profession. It uses a five-point Likert-type scale and contains 40 items. It consists of three dimensions: properties of nursing profession (items 1-18), prefer for nursing profession (items 19-31), and general position of nursing profession (items 32-40). Each item in the scale was scored from 1 to 5, but items 21, 23, 25, 26, 28, 30, 34, and 38 were scored in reverse. A high score indicates that attitudes toward the nursing profession are more favorable. The Cronbach's α value for the total scale was 0.91. In our study, the Cronbach's α value for the total scale was 0.90.

The Scale of Nursing Career Choice (SNCC): This scale was developed by Zysberg and Berry (11) to assess reasons for the career choices of nursing students. Onler and Saracoglu (12) conducted the Turkish validity and reliability study of the scale. The Turkish version of the scale consists of 17 items and 2 subdimensions, namely, occupational compliance (1) and vital causes (6). Each item in the Likert-type scale was rated between 0% and 100%. Since the scale is not used for diagnostic purposes, the obtained score ranges were interpreted. The Cronbach's α value for the total scale was 0.79. In our study, the Cronbach's α value for the total scale was 0.85.

Motivation Sources and Problems Scale (MSPS): The scale was developed by Acat and Kosgeroglu (13) to determine the motivation sources and problems of nursing students. The scale comprises 24 items and 3 subdimensions including intrinsic motivation (1), extrinsic motivation (13), and negative motivation (5). The scale is a five-point Likert type, and the items in the negative motivation subdimension are scored in reverse order. The score of each subdimension is determined by taking the arithmetic average of the scores obtained from the items of the subscale. A high score indicates a high level of motivation. The

minimum and maximum scores are 11 and 55 for the intrinsic motivation subdimension, 5 and 25 for the extrinsic motivation subdimension, and 8 and 40 for the negative motivation subdimension, respectively. The Cronbach's α value for the total scale was 0.82. In our study, the Cronbach's α value for the total scale was 0.88.

Data Collection

Data were obtained using a face-to-face interview method. The interviews lasted approximately 20-25 min.

Statistical Analysis

Statistical analysis was done using the SPSS 22 package program. Number, percentage, minimum, maximum, median, mean, and standard deviation values were used for descriptive analysis. Normal distribution was evaluated using the Kolmogorov-Smirnov test. The independent t and Mann-Whitney U tests were used to compare two groups with normal and non-normal distributions, respectively. Meanwhile, One-Way analysis of variance and Kruskal-Wallis tests were used to compare three and more groups with normal and non-normal distributions, respectively. The strength and relationship direction between two variables were determined using the Pearson's and Spearman's correlation coefficients. A value of $p<0.05$ was considered to be statistically significant.

Ethical Considerations

The authors declare that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013). Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Board of the University Health Sciences Turkey (18/322). Authors' permissions were obtained for the use of the scales. After the participants were informed about the study, data were collected from those who agreed to participate. The study was conducted on a voluntary basis.

RESULTS

Table 1 shows the descriptive characteristics of the participants. The mean age of the participants was 21.1±1.6 years, and 87.4% of them were women. Primarily, 55.9% of participants chose nursing because of the guarantee of employing with respect to career choice. Of the participants' mothers, 48% graduated from primary school, and 37.1% of the fathers graduated from high school. More than half (63.2%) of the participants had a monthly family income status of equal to the outcome.

Table 2 shows the comparison of the difference between class levels of participants and attitudes toward the nursing profession, career choice, motivation sources, and problems. A statistically significant difference among class levels was noted on the following items: attitudes toward the nursing profession, properties of nursing profession, prefer for nursing profession, nurse career choice, occupational compliance, and vital causes ($p<0.05$). A statistically significant difference among class levels was found in the negative motivation subdimension of the MSPS.

Table 3 shows the comparison of gender differences across attitudes toward the nursing profession, nurse career choice, motivation sources, and problems. A statistically significant difference was found between genders in attitudes toward the

Table 1. Distribution of the descriptive characteristics of the participants (n=302)

	n	%
Class levels		
I	118	39.1
II	102	33.8
IV	82	27.1
Gender		
Female	264	87.4
Male	38	12.6
Reason for career choice*		
Guarantee of employing	169	55.9
Helping others	130	43
Making a career	91	30.1
Having a health relative	83	27.4
Mother education level		
Literate	21	7.0
Primary school	146	48.3
Secondary school	35	11.6
High school	78	25.8
University	22	7.3
Father education level		
Literate	14	4.6
Primary school	74	24.5
Secondary school	34	11.3
High school	112	37.1
University	68	22.5
Income level		
Less than expense	34	11.3
Equal to expense	191	63.2
More than expense	77	25.5

*The participants answered in multiple choices

nursing profession, properties of nursing profession, prefer for nursing profession, general position of nursing profession, occupational compliance, motivation, intrinsic motivation, extrinsic motivation, and negative motivation ($p<0.05$).

Table 4 shows the effect of participants' attitudes toward the nursing profession on nurse career choice, motivation sources, and problems. A statistically significant positive correlation was found between attitudes toward the nursing profession and nursing career choices, occupational compliance, motivation, intrinsic motivation, extrinsic motivation, and negative motivation ($p<0.05$).

DISCUSSION

The study aimed to determine the relationship of career choice, motivation, and nursing students' attitudes toward the profession. Career choice is defined as the process where individuals choose one occupation over another in the presence of alternative options and individual preferences (14). Students' attitudes toward the nursing profession and factors such as intrinsic, extrinsic, sociodemographic, and interpersonal are the main factors affecting students' career choices (15). In our study, we found a positive correlation of students' attitudes toward the nursing profession on nurse career choice, occupational

Table 2. Comparison of the difference between attitudes toward the nursing profession, nurse career choice, motivation sources, and class level problems (n=302)

Scales	Class I	Class II	Class IV	Statistics	p value
	Median (min-max)	Median (min-max)	Median (min-max)		
ASNP (mean ± SD)	157.6±19.1	163.5±15.6	159.2±16.7	3.266*	**0.040**
Properties of nursing profession	80.0 (32.0-90.0)	84.0 (54.0-90.0)	85.5 (56.0-90.0)	8.456**	**0.015**
Prefer for nursing profession (mean ± SD)	46.0±8.1	47.9±8.7	44.1±8.8	4.609*	**0.011**
General position of nursing profession	33.0 (17.0-42.0)	34.0 (17.0-39.0)	34.5 (25.0-38.0)	1.624**	0.444
SNCC (mean ± SD)	60.9±16.2	57.3±16.3	51.6±14.3	8.345*	**<0.001**
Occupational compliance	68.6 (12.7-99.1)	66.3 (10.0-100.0)	59.1 (9.1-99.1)	7.004**	**0.030**
Vital causes	52.5 (5.0-100.0)	44.1 (3.3-91.6)	39.1 (13.3-66.6)	32.266**	**<0.001**
MSPS	85.0 (57.0-120.0)	93.0 (56.0-120.0)	93.0 (60.0-120.0)	5.759**	0.056
Intrinsic motivation	41.0 (15.0-55.0)	42 (18.0-55.0)	39.5 (17.0-55.0)	3.266**	0.195
Extrinsic motivation	20.0 (5.0-25.0)	21.0 (9.0-25.0)	21.0 (10.0-25.0)	2.893**	0.235
Negative motivation	28.0 (8.0-40.0)	31.0 (8.0-40.0)	34.0 (19.0-40.0)	23.469**	**<0.001**

*One-Way analysis of variance test, **Kruskal-Wallis test, ASNP: Attitude scale for nursing profession, SNCC: The scale of nurse career choice, MSPS: Motivation sources and problems scale, SD: Standard deviation, min: Minimum, max: Maximum

Table 3. Comparison of the difference between attitudes toward the nursing profession, nurse career choice, motivation sources, and gender level problems of participants (n=302)

Scales	Female	Male	Statistics	p value
	Median (min-max)	Median (min-max)		
ASNP (mean ± SD)	162.0±16.1	146.1±19.8	5.472*	**<0.001**
Properties of nursing profession	84.0 (32.0-90.0)	72.0 (38.0-90.0)	-4.978**	**<0.001**
Prefer for nursing profession (mean ± SD)	46.5±8.5	43.3±8.3	2.163	**0.031**
General position of nursing profession	34.0 (17.0-42.0)	32.0 (23.0-38.0)	-5.017**	**<0.001**
SNCC (mean ± SD)	57.8±15.9	52.9±17.1	1.723	0.086
Occupational compliance	66.3 (9.1-100.0)	48.6 (12.7-95.4)	-2.678**	**0.007**
Vital causes	45.0 (3.3-100.0)	46.6 (3.3-100.0)	-0.977**	0.328
MSPS	92.0 (56.0-120.0)	78.0 (57.0-120.0)	-4.332**	**<0.001**
Intrinsic motivation	41.0 (15.0-55.0)	34.5 (17.0-55.0)	-2.786**	**0.005**
Extrinsic motivation	21.0 (5.0-25.0)	18.0 (10.0-25.0)	-4.005**	**<0.001**
Negative motivation	31.0 (8.0-40.0)	26.0 (14.0-40.0)	-3.356**	**0.001**

*Independent t-test, **Mann-Whitney U test, ASNP: Attitude scale for nursing profession, SNCC: The scale of nurse career choice, MSPS: Motivation sources and problems scale, SD: Standard deviation, min: Minimum, max: Maximum

Table 4. Comparison of the relationship between nurse career choice, motivation sources, and problems with attitudes toward the nursing profession (n=302)

		SNCC	Occupational compliance	Vital causes	MSPS	Intrinsic motivation	Extrinsic motivation	Negative motivation
ASNP	r	0.420*	0.631**	-0.096**	0.730**	0.736**	0.597**	0.239**
	p	**<0.001**	**<0.001**	**0.097**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Properties of nursing profession	r	0.220**	0.321**	-0.126**	0.465**	0.465**	0.456**	0.116**
	p	**<0.001**	**<0.001**	**0.029**	**<0.001**	**<0.001**	**<0.001**	**0.044**
Prefer for nursing profession	r	0.551*	0.706**	-0.068**	0.707**	0.734**	0.493**	0.245**
	p	**<0.001**	**<0.001**	**0.241**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
General position of nursing profession	r	0.317**	0.377**	-0.009**	0.481**	0.444**	0.445**	0.197**
	p	**<0.001**	**<0.001**	**0.872**	**<0.001**	**<0.001**	**<0.001**	**0.001**

*Pearson's correlation test, **Spearman's correlation test, ASNP: Attitude scale for nursing profession, SNCC: The scale of nurse career choice, MSPS: Motivation sources and problems scale

compliance, motivation, intrinsic motivation, extrinsic motivation, and negative motivation. These findings were supported by other studies (15,16).

Our study revealed that first-year students were more likely to choose the nursing profession and found the profession more suitable than other classes. Similarly, studies of Grainger and Bolan (17) and Miers et al. (18) found that students have a quite positive image of nursing in their first year of education and believe in the importance of nursing research and nurses' role in policy development.

With respect to career choice, students in our study chose nursing because of the guarantee of employing, helping others, having a healthy relative, and making a career in nursing. These results also corroborate with a previous study (17). In developed and prosperous countries, although there are internal reasons such as interest, professional appeal, being a health professional, personality traits, liking people, living in developing societies, work guarantee, economy, family influence, pressure, and score, external choice seems to be more effective (18). The internal reasons are preferable in Turkey, whereas external causes influenced some Asian and European countries predominantly (19).

In our study, it was determined that fourth-year nursing students who had experienced applied clinical practice were negatively motivated toward the profession. This occurs as they share their clinical experience with nurses who have a high patient number, heavy workload, long shift, and uncertain role experience and have used complex tools and equipment (20).

The positive progress of the training process will help nursing students to better adapt to their future professional life and find satisfaction in their professions (21). In our study, positive attitudes toward the characteristics of the nursing profession are higher in nursing students in their last year. Changes in students' perceptions as they progress through the nursing program have been noted in literature. Sand-Jecklin and Schaffer (22) found that 95% of students reported that their perceptions had changed over time. Turgay et al. (23) also stated that most of the nursing students had negative opinions against nursing before starting school and that these thoughts increased positively and partially during the education process.

Gender stereotyping of profession is still evident today. It is thought that professions such as teaching and nursing, which employ the assumed caring and subtle character of women, are viewed suitable for women by many societies (24). In our study, it was determined that gender affected attitudes toward profession and positively affected attitudes toward profession, attitudes toward the characteristics of profession, and preference for profession. These results are largely similar to the studies conducted in other countries (25). The study shows that men continue to encounter much prejudice and many social barriers when they go into the nursing profession.

In our study, a positive attitude toward the profession is mostly found in first-year students. It is largely similar to studies conducted in other countries (26). A cross-sectional study conducted on 132 nurses in Israel reported that nurses perceived their profession positively (27). In another study, the perceptions of 100 nursing students were found to be positive in Jordan (6). In our study, students who were new to nursing education relate their perspective of nursing to the school. It is important to show that the attitudes of the Turkish society toward the nursing profession have changed positively.

Choosing a profession is an important decision in an individual's life, and many factors affect the individual in this decision process. A positive attitude toward the profession is an important factor affecting the choice of profession. In our study, a positive relationship was found between attitudes toward the nursing profession and the choice of profession. No study was found to determine the relationship between ASNP and SNCC by using valid tools. In the studies of Guducu Tufekci and Yildiz (28) and Bölükbaş (29), 52.7% and 52.3% of nursing students chose the nursing profession willingly, respectively. If nursing learners willingly chose the profession and have positive attitudes toward the profession, then they can contribute to improve the nursing profession. It is thought that choosing the profession willingly and positive attitude toward the profession could contribute to the development of the nursing profession.

In our study, a statistically significant positive correlation was found between attitudes toward nursing profession and motivation. Similarly, the study of Korkmaz and Ipekçi (30) found that students who were satisfied with the nursing profession have higher internal, external, and occupational learning motivation scores. Considering that high motivation of students will be an important factor in creating and maintaining a positive education environment, it is important to allow students to choose the nursing profession voluntarily.

CONCLUSION

The findings in this study demonstrated that first-year students have more positive attitudes toward the nursing profession than other classes. It is thought that it will be beneficial to conduct further studies to determine the related factors that cause the decline of motivation of students who are in undergraduate nursing education over time. Female nursing students are still more likely to choose the nursing profession in Turkey, and negative motivations for choosing nursing include personal characteristics, such as being incompatible with their personal interests. To reduce the gap between the numbers of male and female students, male nurses could become positive role models by providing information to high school students about the work they do in the hospital.

The nursing profession is facing great staffing shortages, so nursing institutions must show apprentice nurses with positive attitudes toward the profession throughout nursing school. The findings of this study show that for fourth-year nursing students, both school and hospital administrators could help students better understand their future jobs by emphasizing motivation sources such as intrinsic and extrinsic motivations.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Board of the University Health Sciences Turkey (18/322).

Informed Consent: After the participants were informed about the study, data were collected from those who agreed to participate. The study was conducted on a voluntary basis.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.S., E.G., M.E.E., Design: D.S., E.G., M.E.E., Data Collection or Processing: D.S., E.G., M.E.E., Analysis or Interpretation: D.S., E.G., Literature Search: D.S., E.G., M.E.E., Writing: D.S., E.G.

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Comparison of the Long-term Outcomes of Combined Phacovitrectomy and Sequential Surgeries for Macular Hole and Cataract

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Abstract

Objective: This study aimed to compare the long-term functional and anatomical outcomes of combined phacovitrectomy and sequential vitrectomy and cataract surgery for macular hole (MH) and cataract.

Methods: This retrospective comparative study analyzed the medical records of 58 patients who underwent phaco vitrectomy (n=24) or sequential surgery (n=34) for MH and cataract between March 2014 and March 2016. Patients were divided into the combined surgery group, which underwent combined surgery for MH and cataract extraction, and the sequential surgery group, which underwent vitrectomy first, followed by cataract extraction. The primary outcome measures were the best-corrected visual acuity (BCVA) before surgery and at 3, 6, 12, and 24 months after surgery and successful hole closure.

Results: A total of 58 patients were included in this study. The change in BCVA at 3 months after surgery was significantly better in the combined surgery group than in the sequential surgery group. However, no significant difference was found between the groups at 6, 12, and 24 months after surgery. Cataract surgery was performed at 4.9±1.2 months after the first surgery (vitrectomy) in the sequential surgery group. In the success group, the rates of hole closure were 95.8% (23/24) and 97% (33/34) in the combined and sequential surgery groups, respectively.

Conclusion: Combined phaco vitrectomy and sequential vitrectomy and cataract surgery are safe and effective methods for treatment of MH and cataract. Although both methods demonstrate similar anatomical and functional success, combined surgery appears superior over sequential surgery because of the early visual improvement, decreased patient morbidity, and lower cost.

Keywords: Macular hole surgery, closure success, cataract

INTRODUCTION

In recent years, treatment of a macular hole (MH) has shown considerable improvement with the use of optical coherence tomography (OCT) in clinical practice. OCT technology was the first to demonstrate that a vitreoretinal surgery (VRS) may improve visual acuity in MH (1). Moreover, advancements in surgical techniques and instrumentations lead to more favorable functional and anatomical outcomes in MH (2).

MH commonly occurs in the elderly population. In cases with coexisting cataract, VRS may be more challenging due to poor surgical view secondary to media opacities. Combined phacovitrectomy is an approved treatment option in patients

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with combined cataract and vitreoretinal disorders (3,4). This approach improves the surgical view, increases postoperative visual rehabilitation, decreases the need for a secondary procedure, and reduces cost.

In addition, cataract development is common in phakic eyes after vitrectomy (5,6). Undesirable physiological effects of irrigation solutions, accidental mechanical injury, or prolonged gas exposure may accelerate cataract formation after surgery (7). In cataract surgery, more accurate and reliable postoperative refractive outcomes were obtained due to the developments in surgical technique, intraocular lens (IOL) formulations, and use of premium IOLs (8). However, cataract surgery is more complicated in vitrectomized eyes. Anatomical changes such as the absence of vitreous support, deeper anterior chamber, unstable lens capsules, posterior capsular plaques, and weakened zonules are the main risk factors for intraoperative complications (9-14).

Previous studies have described anatomical and functional results of both combined and sequential surgeries in MH (15). However, the effect of lens status during surgery on surgical outcomes is still unknown. Thus, this study aimed to compare the long-term functional and anatomical outcomes of combined phacovitrectomy and sequential vitrectomy and cataract surgeries for eyes with coexisting MH and cataract.

METHODS

Study Population

For this retrospective comparative study, we reviewed the charts of patients with both MH and cataract treated between March 2014 and March 2016. This study adheres to the tenets of the Declaration of Helsinki, and patients gave their written permission before surgery. The study was approved by Beyoğlu Institutional Review Board (date: 31/10/2018- decision number: 19/C-1).

This study included 58 patients, with a follow-up duration of at least 24 months. The patients were divided into two groups according to the timing of vitrectomy and cataract surgery: the combined surgery group consists of patients who underwent phacovitrectomy, and the sequential surgery group consists of patients who underwent vitrectomy, followed by cataract surgery. Medical records of each patient were reviewed, and the following data were recorded: age, sex, systemic diseases, follow-up duration, coexisting retinal diseases, intraocular tamponade, intraoperative and postoperative complications [such as intraocular pressure (IOP) elevation, reactions or synechia in the anterior chamber, hyphema, and retinal tears or detachment], and systemic and topical medications. Patients had undergone complete ophthalmologic evaluation, including assessment of visual acuity, IOP measurement using Goldmann applanation tonometry, slit-lamp biomicroscopy, fundoscopy, and OCT before surgery and at 1 day, 1 week, and 1, 3, 6, 12, and 24 months after surgery. At baseline and follow-ups, macular structural assessment was made using Spectralis (Heidelberg Engineering, Heidelberg, Germany). Then, 25-line and 30-degree scans were performed, and the fovea was determined as the center. Gass staging was done based on the preoperative OCT images, and the hole base diameter, maximum hole height, and shortest diameter of the hole opening were calculated. In each patient, preoperative peripheral retinal examination was performed using wide-field lens. The main outcome measure was the best-corrected visual acuity (BCVA) before surgery and at 3, 6, 12, and 24 months after surgery, IOP changes, use of antiglaucomatous medications, and hole closure rates during postoperative visits. Secondary outcome measures were intraoperative and postoperative complications.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: patients who underwent vitrectomy for idiopathic MH between March 2014 and March 2016 and patients with follow-up duration of at least 24 months. The exclusion criteria for all participants were as follows: Any history of refractive or intraocular surgery, history of blunt and penetrating ocular trauma, traumatic MH, retinal detachment associated with MH, uveitis, diabetic retinopathy, glaucoma, age-related macular degeneration, and high myopia (i.e., greater than six diopters).

Surgical Technique

Surgical decisions were made after discussing with the patients the risks and benefits of surgery. As preparation, the periocular skin (with 10% concentration) and conjunctival fornix (with 5% concentration) were wiped with povidone-iodine. All patients received peribulbar anesthesia 10 min before surgery, induced by subtenon injection of 2 mL of lidocaine hydrochloride 20 mg/mL + epinephrine 0.0125 mg/mL combined with hyaluronidase 300 IU. In the combined surgery group, cataract surgery was performed through two corneal incisions: a main incision of 2.6 mm and a side port incision of 0.9 mm. The phacoemulsification method was used for cataract extraction. Foldable, single-piece posterior chamber IOLs (IOL; Zaracom Monofocal 1-piece IOL) were implanted in the bag in most of the patients. However, three-piece IOLs were implanted in the sulcus if needed. A single corneal suture (Ethicon 10-0; Ethicon Inc., San Angelo, TX) was applied to the corneal tunnel. Then, three-port pars plana

vitrectomy was performed with the constellation system (Alcon Laboratories, Inc., Fort Worth, TX) using 23-gauge valved trocars, and the vitreous gel and posterior hyaloid were removed. The internal limiting membrane (ILM) was stained with a brilliant blue solution and peeled from an area within 2-3 disc diameters from the fovea using forceps. ILM peeling was performed starting from the temporal region to minimize the risk of damaging the papillomacular bundle. The retinal periphery was examined with a wide-angle imaging system after the procedure, and laser photocoagulation (Purepoint® 532 nm Laser) was performed if retinal tears were found. Following the liquid-air exchange, longer-acting gases (C3F8 or SF6) were used to buffer the hole. All surgeries have been performed by the same surgeon (Z.A).

In the sequential surgery group, MH surgery was performed following the same method, and cataract surgery was performed when the cataract caused visual impairment during follow-up. For each patient, intraoperative and postoperative complications were noted. All patients were advised to maintain a face-down position as much as possible 1 week after MH surgery. Standard anti-inflammatory, antibiotic, and, if necessary, anti-glaucomatous treatments were prescribed within 1 month of surgery. In case of an anterior chamber reaction, an anti-inflammatory drug was administered more often.

Statistical Analysis

All statistical analyses were done using SPSS Statistics version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Visual acuities were converted to logarithm of the minimal angle of resolution units. Data normality was assessed using Kolmogorov-Smirnov test. Categorical variables were recorded as numbers and numerical variables as mean and standard deviation. Depending on the variable type, data were analyzed by Wilcoxon, Mann-Whitney U, and Fisher exact tests. The p value <0.05 was accepted for statistical significance.

RESULTS

A total of 58 patients were included in this study, with 24 patients in the combined surgery group and 34 patients in the sequential surgery group. The mean patient age was 68.3±5.9 and 67.5±6.2 years in the combined and sequential surgery groups, respectively. Sex distribution was similar between two the groups (p=0.76). The demographic characteristics of the patients are summarized in Table 1. The mean follow-up time was 26±2.4 months. No significant difference was found in MH size and the period between the appearance of clinical findings and surgery in both groups (p=0.24, p=0.45, respectively). In the overall study group, 12 cases were in stage 2, 28 cases were in stage 3, and 18 cases were in stage 4 according to the Gass classification. The mean interval between vitrectomy and cataract surgery was 4.9±1.2 months in the sequential surgery group. The mean change in the BCVA at 3 month after surgery was statistically significantly better in the combined surgery group than in the sequential surgery group. No significant difference was noted between the two groups at 6, 12, and 24 months after surgery. Changes in the BCVA over time in the two groups are presented in Figure 1. The rates of hole closure in

Table 1. Characteristics of patients operated on using a combined surgery or a consecutive surgery

	Combined group n=24	Consecutive group n=34	p value
Gender (M/F)	11/13	16/18	0.76
Age (years)[a]	68.3±5.9	67.5±6.2	0.81
Mean size of MH (μm)	424 ± 128	431 ± 138	0.24
Duration of MH (months)	5.2±1.3	5.8±1.5	0.45
Mean BCVA (LogMAR)	-	-	-
Preoperative BCVA	0.89±0.21	0.87±0.24	0.69
Postoperative BCVA at 3rd months	0.33±0.18	0.69±0.16	**<0.05**
Postoperative BCVA at 6th months	0.30±0.17	0.31±0.20	0.75
Postoperative BCVA at 12th months	0.31±0.19	0.32±0.21	0.77
Postoperative BCVA at 24th months	0.31±0.18	0.31±0.18	0.81
Mean BCVA change (LogMAR)	-	-	-
At 3rd months after surgery	0.56±0.20	0.18±0.23	**<0.05**
At 6th months after surgery	0.59±0.19	0.56±0.19	0.55
At 12th months after surgery	0.58±0.21	0.55±0.21	0.61
At 24th months after surgery	0.58±0.20	0.56±0.20	0.58

[a]Mean ± standard deviation, M: Male, F: Female, MH: Macular hole, BCVA: Best-corrected visual acuity, LogMAR: Logarithm of minimal angle of resolution

the overall study group, combined surgery group, and sequential surgery group were 96.5% (56/58), 95.8% (23/24), and 97% (33/34), respectively. During vitrectomy in the combined surgery group, three patients had retinal tears, and one patient developed retinal detachment. In the sequential study group, four patients had retinal tears, and retinal detachment was observed in one patient. Retinal tears were treated with endo-photocoagulation, and routine surgical procedures were performed to treat the detached retina.

During cataract surgery. Run-out capsulorhexis in two cases and posterior capsule rupture in two cases were noted among 24 patients in the combined surgery group. In the sequential surgery group, posterior capsule rupture (n=4), run-out capsulorhexis (n=3), and crystalline lens drop (n=1) occurred during cataract surgery. In the overall study group, 10 patients (6 in the combined group and 4 in the sequential group) had IOP elevation, which responded to antiglaucomatous medication. However, no significant difference in IOP levels was found between the groups at 1, 3, 6, 12, and 24 months after surgery. As endotamponade, C3F8 gas was used in 20 (83.3%) and 25 (73.5%) cases and SF6 gas was used in 4 (16.7%) and 9 (26.5%) cases in the combined and sequential surgery groups, respectively.

DISCUSSION

As demonstrated in previous literature and in this study, combined phacovitrectomy and sequential vitrectomy and cataract surgery are both safe and effective methods in patients with coexisting cataract and MH (16). Some authors have attempted to describe the best surgical method in MH surgery to reach a closure rate higher than 90% (17,18). Cataract formation that causes decreased vision after successful VRS is commonly seen in MH. Nuclear sclerosis following vitrectomy has been reported to occur in 75%-90% of patients with MH

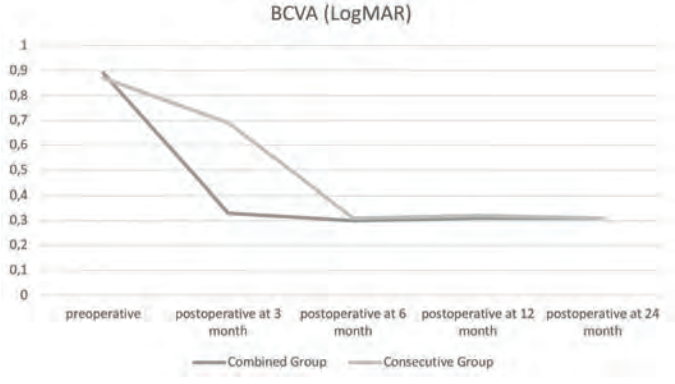

Figure 1. The graph shows the BCVA change of both groups over time
BCVA: Best-corrected visual acuity, LogMAR: Logarithm of minimal angle of resolution

(19,20). Lens opacities may cause difficulty in the visualization of the ILM during surgery. Thus, inadvertent trauma to the neurosensory retina may occur due to the excessive amount of force applied during ILM peeling (21). Combined phaco vitrectomy has many advantages for both the patient and surgeon (22,23). The patient undergoing combined surgery will have fewer visits and will not experience perioperative stress for a second time. By contrast, cataract surgery in vitrectomized eyes is more challenging for surgeons. Zonular weakness, fragile posterior capsule, and unstable anterior chamber are factors that cause difficulties and complications during cataract surgery in vitrectomized eyes (23). In this study, a few complications, including runout capsulorhexis, posterior capsule rupture, and crystalline lens drop, were noted during cataract surgery in the sequential surgery group. Therefore, it is a good surgical option to combine vitrectomy with phacoemulsification in patients with coexisting cataract and MH. Retinal imaging will be more convenient during surgery after cataract removal. However, surgeons should consider the possibility of corneal edema after phacoemulsification in combined surgeries, which impairs retinal visualization. In addition, some authors have emphasized that postoperative inflammation may be more common in combined surgeries, and complications such as posterior synechia, optic capture, and anterior chamber reaction are not rare (24). They have also noted that these postoperative findings might be minimized by using anti-inflammatory drugs and appropriate positioning. In this study, we did not observe these postoperative complications, except anterior chamber reaction in four patients in the combined surgery group.

In this study, functional and anatomical outcomes in both study groups were similar. The mean change in the BCVA at 3 months after surgery was significantly better in the combined surgery group than in the sequential surgery group. However, this significant difference was not observed in other study time points because the mean change in the BCVA after cataract surgery increased statistically significantly in the sequential surgery group and BCVA improvement was similar between the two groups at 6, 12,18, and 24 months after surgery.

Study Limitations

The limitations of our study are its retrospective design and small sample size. The lack of data with regard to preoperative cataract grading is another limitation. A 24-month follow-up period is a strong aspect of the study. Prospective studies evaluating the effect of combined surgery on anterior segment structures are needed to clarify the corneal changes after surgery.

CONCLUSION

Combined phacovitrectomy and sequential vitrectomy and cataract surgery are both safe and effective methods in the treatment of coexisting MH and cataract. Although both methods are similar in terms of anatomical and functional success, combined surgery has the advantages of early visual improvement, decreased patient morbidity, and reduced cost. In addition, combined surgery appears advantageous because more cataract surgery complications were encountered in the sequential surgery group.

Ethics

Ethics Committee Approval: The study was approved by Beyoğlu Institutional Review Board (date: 31/10/2018- decision number: 19/C-1).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.A., Concept: G.D., Design: H.G., Data Collection or Processing: S.Ç., Ş.Ö., Analysis or Interpretation: G.D., S.Ç., M.A., Literature Search: G.D., Z.A., Writing: G.D., S.Ç.

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Epidemiological Investigation of Patients with Advanced-age Femoral Neck Fracture and Evaluation of Surgical Results

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Abstract

Objective: The investigation of the epidemiological status of patients who underwent partial hip replacement is necessary by evaluating their postoperative status based on the hip score so as to examine the effect of additional diseases on postoperative recovery and survival.

Methods: A total of 99 patients who underwent partial hip replacement between September 2013 and 2017 for femoral neck fracture were included in the study. Preoperative diabetes status and presence of additional diseases were examined. Harris scoring form was filled up by all patients. Osteoporosis treatment and additional fracture were evaluated at the final follow-up examination.

Results: The mean age of the 99 study subjects [36 (36.4%) men, 63 (63.6%) women] of all, 18 (18.2%) patients had diabetes and 12 (12.1%) had postoperative fractures. In addition, 17 (17.2%) patients received regular osteoporosis treatment and 4 patients (4.1%) were diagnosed with malignancy from the femoral head. Additional diseases were recorded in 21 (21.2%) patients. The mean Hip Harris score of the patients was 53.62±12.71. A total of 22 (22.2%) patients died during the follow-up. Exitus was significantly lower in patients with high postoperative Harris score ($p<0.001$). No differences were noted between the alive and dead patients with respect to the factors of age, sex, diabetes, additional fracture, and other diseases. Exitus was significantly lower in patients receiving regular osteoporosis treatment ($p=0.001$). No difference was noted in terms of living additional fracture, age, and Harris score. The sex of the patient had no significant effect on the Harris score.

Conclusion: The most important factors affecting survival in patients who were followed up for femoral neck fracture included the high postoperative Harris score, regular osteoporosis treatment received by the patients, and additional fracture experiences.

Keywords: Collum femoris fracture, partial hip replacement, osteoporosis, epidemiology

INTRODUCTION

Femoral neck fractures are commonly encountered injuries in the orthopedic practices and can result in significant morbidity and mortality among elderly. Osteoporosis and neurological disorders are one of the most important risk factors that affect not only women but also men of advanced ages. Femoral fractures represent an increasing financial burden within the total healthcare system and the society considering the deterioration of mobility, limitation of the quality of life, and reduction in the life expectancy (1,2). Hip fractures can be categorized as intercapsuler femoral neck fractures and trochanteric fractures. According to the American Academy of Orthopedic Surgeons' Evidence-Based Guideline on the management of displaced femoral neck fractures in elderly, either total or partial hip replacement surgery is preferred in relation with the activity of patients, the quality of the bone, and presence of comorbidities (3). Partial hip replacement surgery is the most preferred surgical option for elderly with sustained femoral neck fracture in our country. The Harris Hip score is a clinician-based outcome measure for the postsurgical evaluation of the activity levels of the patients (4). Age and comorbidities are the factors that have an important impact on the Harris Hip scores and life expectancy

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(5). Further epidemiological investigations are required to evaluate the effects of comorbidities, life quality, and life expectancy for patients who undergo partial hip replacement surgery in our country. The purpose of this study was to evaluate the patients who underwent partial hip replacement surgery for femoral neck fracture by means of their Harris Hip score in order to assess the postoperative conditions as well as the effects of the presence of comorbidities and postoperative life expectancy on the well-being of the patients.

METHODS

We evaluated the patients operated for femoral neck replacement during September 2013-2017 by retrospective analysis. A total of 127 patients were included in this study. The study exclusion criteria were the impossibility to reach the patient's relatives, the lack of postoperative follow-up in the 6th month, the lack of the recording of Harris Hip score form, and postoperative wound infection and advanced heart failure. In addition, 99 patients who met the inclusion criteria were included in the study.

The study design was reviewed and approved by the Baskent University Faculty of Medicine Human Research Ethics Committee (K/A 19-408). All investigations conformed to the ethical principles of research, and informed consent for their participation in this study was obtained from all patients.

All patients were approached by means of modified Gibson incision posterolaterally; the outer rotator muscles were reflected and a T-shaped incision was made in the hip capsule to reveal the underlying deep anatomical structures. The physical therapy program was outlined as to when the patient could sit, start the motion of the operated hip, and begin ambulation immediately on the day after the surgery. Postoperative follow-up was performed at 1.5-2 months of the surgery. The Harris Hip score was recorded at postoperative 6th month. Osteoporosis therapy was initiated for patients with the appropriate general medical conditions. The quality of life, the presence of additional fractures, and the stages of osteoporosis treatment were evaluated by means of recalling the patients or the patients' relatives. The patients who received ≥2 years of osteoporosis treatment were accepted as those who were receiving regular osteoporosis treatment. All the patients were diagnosed for the presence of diabetes pre-surgically and chronic renal disease and neurological disease both pre- and post-surgically.

Statistical Analysis

Data were analyzed using the SPSS statistical software (version 17.0; SPSS Inc., SPSS Inc., Chicago, IL, USA). The variations showing parametric distribution were described as mean + standard deviation, while the non-parametric distribution was described as median (minimum-maximum). We decided that the data should be parametric or non-parametric by looking at the Kolmogorov-Smirnov or Shapiro-Wilk tests and the histogram distributions. Chi-square test or Fisher Exact test statistic were used to compare the categorical variables. Quantitative variables were compared using t-test, while chi-square test was applied to compare the qualitative variables. The significance threshold was set at 0.05.

RESULTS

A total of 99 patients were enrolled in this study. The mean age of the patients [36 men (36%), 63 women (63%)] was 81.23+8.34 years. The mean postoperative follow-up period was 41 (8-75) months. A total of 18 patients (18.2%) had diabetes and 12 (12.1%) developed additional fractures later. Only 17 patients (17.2%) received regular osteoporosis therapy. According to the pathology reports, 4 patients (4.1%) were diagnosed with malignancy and 21 patients (21.2%) with neurological diseases and chronic renal diseases. The mean Harris Hip score was 53.62+12.71. A total of 22 patients (22.2%) in this study were exitus during the follow-up period (Table 1).

The postoperative Harris Hip score was significantly greater in alive patients than in exitus patients ($p<0.001$). No significant difference was noted between the alive and exitus groups for the factors of age, gender, diabetes, additional fracture, and comorbidities ($p=0.43$, $p=0.34$, $p=0.72$, $p=0.55$, respectively). All patients who received regular osteoporosis treatment were found to be alive; thus, when compared to exitus patients, osteoporosis treatment showed a significantly better effect on the life expectancy (Table 2). There was no statistically significant difference between the factors of gender and presence of diabetes when additional fractures were concerned ($p=0.051$, $p=0.45$, respectively). Two patients receiving regular osteoporosis treatment had additional fractures, which was not statistically significant ($p=0.051$, $p=0.45$). In addition, no statistically significant difference was detected among the factors of age, postoperative Harris Hip score, and comorbidities by means of additional fractures ($p=0.90$, $p=0.60$, $p=0.71$, respectively) (Table 3). No statistically significant difference was noted between the gender and Harris Hip score (Table 2).

DISCUSSION

Most studies on the determinants of osteoporosis-related fractures have been dedicated to hip fractures in aging population

Table 1. The epidemiological evaluation of the study population									
n	Age	M/F	Harris Hip score	Diabetes mellitus	Osteoporosis treatment	Additional fractures	Comorbidities	Malignity	Exitus
99	81.23±8.34	36/63	53.62±12.71	18 (18.2%)	17 (17.2%)	12 (12.1%)	21 (21.2%)	4 (4.1%)	22 (22.2%)
M: Male, F: Female									

Table 2. The comparison of select parameters between alive and exitus patients			
	Alive	Exitus	p value
n	77	22	-
Age	80.9±8.3	82.4±8.7	0.439
Harris Hip score	59 (IQR=6)	40 (IQR=13)	0.0001
Gender (F/M)	27/50	9/13	0.624
Diabetes (+/-)	16/61	2/20	0.347
Additional fractures (+/-)	9/68	3/19	0.726
Osteoporosis treatment	17/60	0/22	0.011
Comorbidities	15/62	6/16	0.554
Chi-square test or Fisher exact test statistic was used to compare the categorical variables. We decided whether the data should be parametric or non-parametric based on the results of Kolmogorov-Smirnov or Shapiro-Wilk tests and histogram distributions. M: Male, F: Female, IQR: Interquartile range			

Table 3. The relationship between additional fractures and other parameters			
Additional fractures	Present	Not present	p value
Age	81.5±8.5	81.2±8.4	0.906
Gender (M/F)	1/11	35/52	0.051
Diabetes (+/-)	3/9	15/72	0.453
Osteoporosis treatment (+/-)	2/10	15/72	1.00
Harris Hip score	51 (IQR=13)	56 (IQR=16)	0.607
Comorbidities (+/-)	3/9	18/6	0.714
Chi-square test or Fisher exact test statistic was used to compare the categorical variables. We decided whether the data should be parametric or non-parametric based on the Kolmogorov-Smirnov or Shapiro-Wilk tests and histogram distributions. M: Male, F: Female, IQR: Interquartile range			

(6). Studies related to femoral neck fractures and epidemiology are limited and variable in our country (7-9). Literature on the investigation of the distribution of fracture types according to age has revealed that femoral neck fractures occur more frequently in elder patients than trochanteric fractures. Kannus et al. (10) stated that the mean age of male and female hip fracture patients was 69 and 78.9 years, respectively, in a large case series. In our study, since only femoral neck fractures were studied, the age distribution were found to be relatively greater when compared to that in studies inspecting the overall hip fractures.

Gender is another risk factor cited by the literature. The ratio of hip fractures for women has been reported as 68.3-74% (7,10). In our study, the mean ratio of male and female patients was similar to that suggested by the literature. In a study conducted in 2019 in England, 18 malignities were identified among 119 femoral neck fractures; however, no significant difference was recorded between the malignity and cost (11). Only 4 patients had malignity, and no cost-effectiveness analysis was conducted in our study. Overlooking the risk of malignity has a deleterious effect on the cost analysis as well as on the resultant malpractice in our country. In a prospective cohort study of 32,089 patients, Nicodemus et al. (12) specified that diabetes can lead to osteoporosis, which increases the risk of hip fractures. In past studies inspecting the relationship between diabetes and osteoporosis, unlike for type 1 diabetes, type 2 diabetes has been reported to have no association with osteoporosis (12,13). Although diabetes has no significant increasing effect on osteoporosis, the comparison of bone mineral density and preoperative osteoporosis was not examined in the present study. The mortality rate of patients who underwent hip surgery ranged from 3.2% to 35.8% throughout the literature. However, in most of the studies, the rate of mortality was higher when compared to that in the following years (14-16). Similar to that reported in the literature, the mortality rate in our study was 22.2%. In several studies, significant relationships have been defined in relation to the male gender and the presence and number of additional diseases (14,15). However, in our study, no significant relationship was noted among mortality, additional diseases, age, gender, and diabetes. In several studies, postoperative hip-scoring systems were found to have high predictability on the life expectancy (7,8,14,16). Similar to that in the literature, patients with high Harris Hip scores posed a low risk of mortality in our study. In this study, for patients receiving regular osteoporosis treatment, the mortality ratio

was significantly lower when compared to those not receiving regular treatment.

CONCLUSION

The most critical factors for patients to receive surgery in relation with femoral neck fracture include the high Harris Hip score, regular osteoporosis treatment, and the lack of additional fractures affecting the survival rate. In addition, one of the most important benefits of epidemiological evaluation of the femoral neck fractures is to take the necessary precautions to minimize mortality and morbidity due to fractures.

Ethics

Ethics Committee Approval: Baskent University Faculty of Medicine Human Research Ethics Committee (K/A 19-408).

Informed Consent: Informed consent for their participation in this study was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

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ORIGINAL ARTICLE

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Impact of Canalith Repositioning Maneuver with or Without Vestibular Suppressant Therapy on Anxiety Levels among Patients with Benign Paroxysmal Positional Vertigo

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Abstract

Objective: Many studies do not recommend vestibular suppressant as an adjunctive therapy to canalith repositioning maneuver (CRM); nevertheless, it has been proven that those treatment regimens may alter the natural course of treatment by lowering both the anxiety effect and an additive placebo effect. Therefore, we aimed to look for and compare the efficacy of CRM therapy alone with maneuver (M) + vestibular suppressant therapy (M + VST). As a novelty, we used the State-Trait Anxiety Inventory (STAI) to express both the current and underlying anxiety level of the susceptible cases.

Methods: One hundred cases were included in the study and were randomly assigned to either CRM or M + VST groups. Before the therapy, each participant received a 40-item STAI test, and then the select treatment was applied. On the second week, the participants were reevaluated and filled in another STAI.

Results: In CRM, 23 cases were affected from the right side and 27 from the left side. Further, 21 cases received the barbeque M and 29 the Epley maneuver. On the other hand, in M + VST, 19 cases were affected from the right side and 31 from the left side. In addition, 27 cases received the barbeque M and 23 the Epley maneuver. The STAI-State (S) and STAI-Trait (T) results were compared before and after the treatment regimens. Pretreatment scores of STAI-S or STAI-T were not significant between the two groups ($p=0.494$; $p=0.481$). STAI-S and STAI-T scores substantially decreased within the groups after the treatment; in other words, both CRM and M + VST had lower scores after the treatment regimens ($p<0.05$). The posttreatment STAI-S and STAI-T scores were lower in M + VST than that of CRM ($p<0.05$).

Conclusion: VST is not advised in benign paroxysmal positional vertigo; CRMs alone are proven effective. However, there might be of minimal additional therapeutic effects of drug therapy to control the anxiety levels.

Keywords: Vertigo, maneuver, anxiety

INTRODUCTION

Vertigo, sensation of whirling and loss of balance, could be experienced by looking down from a high altitude or in symptomatic cases caused by a condition affecting the inner ear. The most common cause of vertigo is benign paroxysmal positional vertigo (BPPV), which causes anxiety in almost every case and is responsible for 20%-40% of cases (1).

This particular subtype of peripheral vertigo is clearly dependent on postural changes, especially the rotation of the head, and is characterized by nystagmus and repetitive short attacks of severe dizziness. Although it has been thought to be linked to psychiatric disorders such as depression, panic attacks, and other anxiety disorders, medically anxiety does not cause vertigo. What it causes is a combination of three different

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experiences mimicking vertigo as a symptom: dizziness, light headedness, and nausea. On the other hand, vertigo triggers anxiety. Information obtained from the inner ear is processed in the amygdala, infralimbic cortex, and hypothalamus which are also a part of the network system for emotional encoding, particularly the parabrachial nucleus (2).

The State-Trait Anxiety Inventory (STAI) is a psychometric scale consisting of 40 statements. STAI has State (S)-Anxiety and Trait (T)-Anxiety subscales that evaluate different periods/types of anxiety: STAI-S measures state anxiety and deals with how the respondents feel "right now", using items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system, while STAI-T measures the trait anxiety or anxiety level as a part of personal characteristics, including general states of calmness, confidence, and security. The increase in the scores is associated with higher levels of anxiety. The specific attention of all other anxiety questionnaires, other than STAI, is focused on one type of anxiety at the time. However, STAI measures both the current and the trait anxiety (3).

A literature review revealed a study using STAI to measure the anxiety levels of the cases; nevertheless to the best of our knowledge, we found none to compare the anxiety levels after either a canalith repositioning maneuver (CRM) alone or maneuver (M) + vestibular suppressant therapy (VST) (4). It was therefore our intention to carry out a thorough analysis in order to find this specific basis, to contribute to the literature, and thus to assess the efficacy of treatment on anxiety levels more in detail by assessing the STAI subscales.

METHODS

Between February and April 2020, 100 cases (39 male, 61 female) were included in the study, the approval from the local Ethics Committee of Okmeydanı Research and Education Hospital was taken (04.02.2020/48670771-514.10), and informed consent was obtained from all participants.

All cases underwent a detailed otolaryngologic examination. However, in suspected cases, internal medicine and/or neurological consultations were performed to exclude central or metabolic causes of dizziness. Magnetic resonance imaging scans of the brain and internal acoustic canals and Doppler ultrasounds of the neck were also completed if needed.

Each participant underwent pure tone audiometry (PTA) to detect any disorder through the frequencies between 250 and 8000 Hz (Interacoustics AC40, Denmark) and completed STAI-S and STAI-T after PTA.

Finally, videonystagmography and video head impulse tests were performed using ICS Impulse video goggles system (GN Otometrics, Schaumburg, IL, USA). The participants were seated in a well-lit room at a distance of 1 m from a target point on the wall approximately 90 cm above the floor. A pair of glasses with a high-frequency (250 Hz) video camera was positioned to record real-time eye movements. There was also a motion sensor to measure head movements. Before each test, calibration was performed to ensure correct measurement. All tests were carried out by a single professional nurse. Moreover, the head impulses were delivered unpredictably. This was required in regard to both direction and timing. The head impulses were applied with a small amplitude (5°-20°) and high acceleration (1,000°/s^2-4,000°/s^2). To conduct a horizontal semicircular canal testing, the hands of the attendant were placed on the jaw and on top of the head. The participant's head was turned 30° forward in the pitch plane to position the horizontal semicircular canals completely horizontal. Ten to twenty head impulses were delivered to each side. To perform a vertical semicircular canal testing, the hands of the attendant were placed on top of the participant's head, and the fingers were directed toward the anterior semicircular canal to be tested. The chair was rotated 45° to either side and before vertical semicircular canal testing. In order to test the right anterior (RA) and left posterior (LP) semicircular canal, the chair was turned 45° to the left, and the participant was asked to look at the fixation dot. For RA, the participant's head was rotated forward in the pitch plane perpendicular to the wall; and for LP, the participant's head was rotated backward in the pitch plane perpendicular to the wall. For the left anterior canal, the participant's head was rotated forward in the pitch plane perpendicular to the wall, whereas for the right posterior canal, the participant's head was rotated backward in the pitch plane perpendicular to the wall. Vestibulo-ocular reflex saccades of the patient were recorded and transferred to a computer. Corrective saccades were defined as transient (fast) eye movements. Those that occur after the head rotation were referred to as overt saccades, whereas those that occur during the head rotation were referred to as covert saccades.

Before proceeding to the vestibular test, all cases were strictly asked not to continue their vestibular suppressant drug therapy for at least 5 days prior to the test. Exclusion criteria included pediatric age group, vision loss, limited neck movement that loses concentration in the test, ongoing vestibular rehabilitation patients, neurological diseases affecting the central nervous system, psychiatric disorders, and being under vestibular suppressant medications.

Cases were then randomly divided into two groups using a computer-based randomization program (5): CRM and M + VST, both designed as the study group. All cases received the appropriate maneuver in the CRM, whereas in M + VST, maneuver and medication (betahistine dihydrochloride 24 mg BID + dimenhydrinate 50 mg BID) were both applied for at least 1 month. The control examinations of all cases were done 2 weeks after, and a second STAI-S and STAI-T tests were completed for each case.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM SPSS, Turkey) where the continuous data was displayed as the mean ± standard deviation. The normality of the data distribution was assessed using the Shapiro-Wilk test. Student's t-test was used for between-group comparisons of normally distributed parameters, while the paired sample t-test was applied for in-group comparisons. Moreover, descriptive statistics included mean ± standard deviations. Statistical significance was considered to be a p value of lesser than 0.05.

RESULTS

We evaluated the anxiety scores of 100 cases, equally distributed into two groups: 50 for CRM and 50 for M + VST. The mean age of CRM was 50.84±12.49 and the mean age of M + VST was 36.92±10.24. Furthermore, the age comparison between the groups was not significant (p>0.05). In the CRM group, 16 (41.0%) were male and 23 (59.0%) were female, whereas in M + VST group, 34 (55.7%) were male and 27 (44.3%) were female. Likewise, gender between the groups was also not significant (p>0.05) (Table 1).

In CRM, 23 cases were affected from the right side and 27 from the left side (27 posterior, 21 lateral, and 2 superior semicircular canal pathologies). Twenty-one cases received the barbeque maneuver and 29 received the Epley maneuver. On the other hand, in M + VST, 19 cases were affected from the right side and 31 from the left side (26 posterior, 23 lateral, and 1 superior semicircular canal pathology). Twenty-six cases received the barbeque maneuver and 24 received the Epley maneuver.

The STAI-S and STAI-T results were compared before and after the treatment regimens. Pretreatment scores of STAI-T were not significant between the two groups (p=0.692). STAI-S levels in both groups significantly decreased after adequate therapy (p=0.001; p=0.001). STAI-S and STAI-T scores substantially decreased within the groups after the treatment, i.e., both CRM and M + VST had lower scores after the treatment regimens (p=0.001). The posttreatment STAI-S and STAI-T scores were lower in M + VST than that of CRM and were statistically significant (p=0.001) (Table 2).

Table 1. Demographics

	CRM (n=50)	M + VST (n=50)	p
Age (Mean ± SD)	40.84±12.49	36.92±10.24	**0.122**
Gender (n, %)			
Male	16 (41.0%)	34 (55.7%)	**0.219**
Female	23 (59.0%)	27 (44.3%)	

Student's t-test for age, continuity (yates) correction for gender is applied, p<0.01, CRM: Canalith repositioning maneuver-only group, M + VST: Vestibular suppressant therapy + canalith repositioning maneuver group, SD: Standard deviation

DISCUSSION

Anxiety and fear have long been recognized by the clinicians to be associated with vestibular symptoms, namely, loss of balance, dizziness, or nausea, are perceived as frightening, catastrophic, or deadly. Therefore, it is usually imperative to investigate the interface between anxiety and vestibular disturbance (2).

Majority of the vestibular disorders are BPPV, and the mainstay of therapy in BPPV is the canal repositioning maneuver. A single maneuver is effective as high as 70%-90%, and patients are often free from symptoms after a single maneuver. Some additional measures, such as sedation, head vibration during treatment, keeping the head in an upright position for 48 hours to prevent the particles from entering the canal, avoiding lying down with the affected ear for 1 week, wearing a neck collar, and avoiding a positional test examination for about a week after treatment, have been proposed to improve the effectiveness of the treatment (6,7).

Table 2. Intergroup and intragroup comparisons for STAI-T and STAI-S

		CRM (n=50)	M + VST (n=50)	[1]p
STAI-S	**Pretreatment**	64.02±6.89	66.88±5.44	**0.023***
	Posttreatment	32.24±4.15	23.88±2.51	**0.001***
	Difference (%)	31.78±7.60	43.01±6.11	**0.001***
	[2]p	0.001	0.001	
STAI-T	**Pretreatment**	67.98±7.88	68.54±6.07	**0.692**
	Posttreatment	34.18±4.10	24.36±2.68	**0.001***
	Difference (%)	33.80±8.31	44.18±6.81	**0.001***
	[2]p	0.001	0.001	

[1]Student's t-test, [2]Paired sample t-test, *p<0.05, CRM: Canalith repositioning maneuver-only group, M + VST: Vestibular suppressant therapy + canalith repositioning maneuver group, STAI-S: State-Trait Anxiety Inventory-State, STAI-T: State-Trait Anxiety Inventory-Trait

A recent study included 64 cases diagnosed with BPPV. These cases were then grouped into three. In the first group, only CRM was performed, while in the second group, CRM with betahistine 24 mg twice daily was administered for 10 days. In the third group, CRM with dimenhydrinate 50 mg once daily was given for 5 days. Cases were reexamined on the 10th day, showing no superiority of one group over another, suggesting that drugs were no beneficial in the BPPV (8). However, we have not achieved results in accordance with the abovementioned article. The anxiety levels of M + VST was significantly lower than that of the CRM group. Nevertheless, in the clinical practice guideline for BPPV, VST was not routinely recommended for its side effects, such as drowsiness that impedes social life, but it was found helpful in treating symptoms such as nausea or vomiting in severely symptomatic cases. The guideline also advices not to use them in severely symptomatic cases that refuse therapy or become severely symptomatic after a positioning maneuver (9).

Various studies have reported concurrent psychiatric symptoms in some BPPV cases (10,11). The percentage of concurrence is thought to be greater among patients with psychiatric disorders. Moreover, cases that have comorbid psychiatric symptoms may have dizziness even in the absence of objective tests. Those cases refrain themselves from social interactions, and their anxiety level is thought to be more than the healthy population (12). This was the limitation of our study, where psychiatric disorders are excluded.

Published data revealed that vertigo patients had anxiety at a rate between 30% and 73.5%. These reports have used several different methods to identify the level of anxiety such as Hospital Anxiety and Depression scale, STAI, or Beck Anxiety Inventory. Regardless of the different scales that measure anxiety, the anxiety levels were proven higher than that of anxiety disorders in the overall population (13-16). In our study, all of our cases had severe anxiety prior to treatment, but the level of anxiety decreased too much extent 2 weeks after the ongoing treatment.

Recently, owing to the effects of placebo on improved self-control, comprehensive studies have shown the effects of placebo on neuralgia, psychiatric disorders, and neurological diseases such as Parkinson's disease (17,18). These studies showed that the beliefs altered the neural processes and changed the perception and emotion. Although our study was not based on a placebo effect, considering the aforementioned reports and guidelines on the excessive use of drugs in BPPV, our results, on the contrary, have proven that drug therapy administered concurrently with the CRM has helped to relieve anxiety to a much lower extent.

CONCLUSION

VST is not recommended in BPPV; however, CRMs alone are proven effective. Nevertheless, in symptomatic cases, a short-term use of suppressant therapy has been proven effective in controlling anxiety levels.

Ethics

Ethics Committee Approval: Ethics Committee of Okmeydanı Research and Education Hospital was taken (04.02.2020/48670771-514.10).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Evaluation of the Effects of COVID-19 Pandemic Among Patients with Inflammatory Bowel Diseases

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Abstract

Objective: The Coronavirus Disease-2019 (COVID-19) pandemic continues to be a concern, especially to people with chronic diseases across the entire world. During this pandemic, we undertook an investigation to assess how the disease state and medical treatments of inflammatory bowel disease (IBD) are affecting the IBD patients, their risky perceptions, as well as the frequency and course of COVID-19.

Methods: During the pandemic, the information on the course of the disease, medical treatment status of the patients with IBD, and the course of the disease in IBD patients who had COVID-19 were collected via telephonic interview.

Results: A total of 102 IBD patients, including 62 with ulcerative colitis and 40 with Crohn's disease were included in the study. Of these, 52.9% of the patients believed that having IBD was a risk for COVID-19. During the pandemic, 18.6% of the patients did not take their medication regularly for various reasons. Of all, 64.28% of the patients with active disease could not go to the hospital to avoid the risk of acquiring COVID-19 and 4.90% acquired COVID-19.

Conclusion: During the pandemic, both the regular consumption of medicines and the reservations regarding admission to hospitals affect the course of IBD. Therefore, the development of strategic action plans to support and manage changes experienced during the course of this disease is expected to facilitate the management of the disease process in a healthier way for both the physicians and the patients.

Keywords: Inflammatory bowel disease, COVID-19, ulcerative colitis, Crohn disease

INTRODUCTION

Since the first cases were detected in Wuhan, China in December 2019, the new Coronavirus Disease-2019 (COVID-19) Severe Acute Respiratory syndrome-coronavirus-2 (SARS-CoV-2) has affected the entire world population, creating a serious public health issue. Although, initially, it was believed to be a pure respiratory pathogen transmitted via droplets and aerosols, it has also now been observed to cause severe symptoms of the gastrointestinal system (1). The most common symptoms of COVID-19 are fever and respiratory distress. However, a significant proportion of COVID-19 patients also have digestive system symptoms such as changes in their bowel habits, diarrhea, vomiting, and anorexia (2). SARS-CoV-2 enters the cells via angiotensin-converting enzyme 2 (ACE2) receptor (3). The ACE2 receptor is expressed in several organs, such as the lung, tongue, pancreas, and intestines (4). Gastrointestinal symptoms (GIS) are caused by the ACE2 expression in the intestine (5).

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of inflammatory bowel diseases (IBDs) and are characterized by remission and exacerbation episodes (6). It is understandable that patients with IBD experience weakness and are worried about acquiring COVID-19 infection during the

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pandemic period due to the nature of the disease transmission and the immunomodulatory drugs used in the treatment process.

SARS-CoV-2 has spread rapidly to the entire world from China, after which the World Health Organization declared the COVID-19 pandemic on March 11, 2020. As in almost all countries of the world, extremely serious and strict public health regulations and strict quarantine measures have been taken in order to prevent the further spread of the disease as well as to provide the treatment to patients diagnosed with COVID-19. During this process, it has become difficult for patients with chronic diseases, such as IBD patients, to manage their medical follow-up and treatment. In addition, the combat against COVID-19 has gained priority among all healthcare professionals at all levels, which has made it difficult for non-COVID-19 patients to reach health institutions for treatment. Patients with IBD may need additional endoscopic procedures and several more potent medical treatments, especially during the exacerbation periods. However, as in several countries, routine endoscopic procedures were temporarily suspended in Turkey with the recommendations of health authorities and only emergency endoscopic procedures. This situation may have resulted in a delay in the routine planned procedures, and more effective treatments plans had to be initiated in case of disease exacerbation. Due to the ensuing concerns about the risk of COVID-19 transmission on their illnesses and medications, IBD patients are likely to face difficulties in accessing the clinical centers and physicians for follow-up. In addition, some patients may have discontinued or postponed their medical treatment during this period.

In this study, we aimed to investigate the extent to which the disease status and medical treatments of IBD patients were affected during the COVID-19 pandemic, as well as their perception about infection risk and the frequency and course of COVID-19.

METHODS

This study was approved by the Prof. Dr. Cemil Taşçıoğlu City Hospital/Local Human Research Ethics Committee, and all procedures conducted in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Local Ethics Committee (12/05/2020 decision no: 156).

All subjects included in this study agreed to their participation with their informed consent for the processing and collection of data for scientific purposes. A detailed questionnaire was administered to all subjects by telephone or email.

Patients Selection

Patients with follow-up medical files from the gastroenterology outpatient clinical department of the institution, and who were aged >18 years and were clinically, endoscopically, radiologically, and histopathologically diagnosed with IBD (UC or CD) were included in the study.

Patients with an uncertain diagnosis of IBD, age <18 years, with incomplete information in their medical files, and those who could not be contacted via phone or who did not agree to participate in the study or who had incomplete answers to the questions were excluded from the study. Finally, 102 (71.83%) of the 142 patients who were followed up with UC and CD were included for study analysis because they met the inclusion criteria (Table 1).

The subjects were asked whether there was an exacerbation related to IBD diseases in the 3 month period from March 15, 2020 to June 15, 2020, when COVID-19 cases are detected in our country, about their endoscopy needs and accessibility to the hospital, changes in their medical treatments and the affecting parameters, the other diseases and the medical treatments used; the patient perception about the risk to COVID-19 infection in terms of their illnesses and medical treatments, and the disease-related parameters (disease involvement site) and whether they were diagnosed with COVID-19 during this period, their requests for follow-up, symptoms of those diagnosed with COVID-19, and the course of the disease and the management of the drugs were questioned.

Harvey Bradshaw for CD patients and the partial Mayo score for UC were applied to assess the disease activity of the subjects.

Statistical Analysis

Data were analyzed using the statistical package program (SPSS 20.0). The mean ± standard deviation and median for descriptive data and continuous variables and the numbers and percentages for categorical variables were presented. Shapiro-Wilk test was applied to evaluate the normal distribution of the data. In the analysis of the changes within the data, the ones selected according to the distribution characteristics, Pearson's chi-square test, Fisher exact chi-square test, McNemar test, Wilcoxon test, and t-test in dependent groups were used. During the evaluation of the results, $p \leq 0.05$ was considered to be statistically significant.

RESULTS

A total of 102 IBD patients [62 (60.8%) UC and 40 (39.2%) CD] were included in the study. The mean age of the UC group was 40.87±13.81 years and that of the CD group was 40.20±12.75 years; the disease duration of UC and CD was 6.29±6.06 and 6.58±6.70 years, respectively. The demographic data are shown in Table 1.

Table 1. The clinical-demographic data of the study groups

	CD (n=40) n (%)	UC (n=62) n (%)
Age		
≤24	6 (15)	8 (12.9)
25-34	5 (12.5)	14 (22.6)
35-44	16 (40)	15 (24.2)
45-54	9 (22.5)	13 (21.0)
55-64	3 (7.5)	10 (16.1)
≥65	1 (2.5)	2 (3.2)
Gender		
Female	23 (57.5)	28 (45.2)
Male	17 (42.5)	34 (54.8)
Occupation		
Unemployed	3 (7.5)	0 (0.0)
Retired	3 (7.5)	10 (16.1)
Housewife	13 (32.5)	16 (25.8)
Self-employment	4 (10)	4 (6.5)
Other	17 (42.5)	32 (51.6)
Marital status		
Married	30 (75)	45 (72.6)
Single	10 (25)	17 (27.4)
Education status		
Primary education	20 (50)	30 (48.4)
High school	16 (40)	20 (32.3)
University	4 (10)	12 (19.4)
Previous operation		
Yes	8 (20)	3 (4.8)
No	32 (80)	59 (95.2)
Age at diagnosis		
≤24	9 (22.5)	14 (22.6)
25-34	13 (32.5)	20 (32.3)
35-44	11 (27.5)	13 (21.0)
45-54	5 (12.5)	9 (14.5)
55-64	1 (2.5)	5 (8.1)
≥65	1 (2.5)	1 (1.6)
Duration of disease		
3≤	14 (35.0)	29 (46.8)
4-7	17 (42.5)	16 (25.8)
8-11	2 (5.0)	4 (6.5)
12≥	7 (17.5)	13 (21.0)

CD: Crohn's disease, UC: Ulcerative colitis

Comparison of the data about the patients' weight and body mass index (BMI) before and during the pandemic revealed no statistically significant difference in the UC groups, but both the weight and BMI in the CD group had increased during the pandemic than before it (p=0.010, p=0.022, respectively).

When IBD was considered as a single group and the patients were questioned whether they consider the risk of acquiring COVID-19 as a high risk due to their disease, 54 (52.9%) of the patients believed that IBD was a risk for COVID-19 (Table 2). The age, gender, year of illness, age of diagnosis, marital status, educational status, and surgery status did not have a statistically significant difference in terms of perception about the risk of acquiring COVID-19 as a high risk. In addition, when questioned whether the drugs used could increase the risk of COVID-19 infection, 15 (14.7%) of the patients answered were affirmative, and the most common drug used by these patients was meselasine.

During the pandemic, 83 (81.4%) of the patients took their medications regularly. In 19 (18.6%) patients with irregular drug usage, the most common reason for not being regular was the difficulty in accessing drugs (31.57%), no specific reason (21.05%), due to active infection (15.78%), the belief that the drugs suppress the immune system (15.78%), forgetfulness (15.78%), and refusing to go to the hospital for infusion due to the risk of COVID-19 (5.26%). Six (5.9%) patients decreased their self-medication doses without consulting any physician, but did not discontinue it. Seven (36.8%) of 19 people who did not consume the drugs regularly faced disease exacerbation in the last 3 months, and 3 (42.8%) of these 7 subjects changed their medications without consulting any physician.

No significant difference was noted in terms of perceiving the risk of developing COVID-19 as a high risk between subjects who took or did not take regular medications and those who changed or did not change their medications on their own without consulting a physician. However, it was found that patients who changed their self-medication doses thought that they had a greater risk of acquiring COVID-19 (p=0.001).

In the last 3 months, 24 (17 UC and 7 CD, 23.5%) patients experienced disease exacerbation and 14 patients (58.33%) did not go to the hospital. COVID-19 infection (64.28%) and not getting an appointment (21.42%) were the most common reasons for not going to the hospital for treating the exacerbation. Considering

the onset of symptoms and the duration of hospital admission, 4 (40%) patients were admitted to the hospital immediately, 3 (30%) patients were admitted within 1 week, and 3 (30%) were admitted within 2-3 weeks (Table 3). Only 3 (12.5%) patients who experienced disease exacerbation underwent an endoscopic procedure.

Cortisone treatment was initiated as follows: initial doses of cortisone in 6 (25%) of the 24 patients who experienced an exacerbation during the pandemic; 3 (50%) patients 20 mg/day, 2 (33.3%) patients 32 mg/day, and 1 (16.7%) patient 40 mg/day. In one patient, cortisone treatment was initiated before the pandemic and the dose reduction was started during pandemic period. In other words, 7 (6.9%) patients received cortisone treatment in total. No COVID-19 infection was recorded in any of these patients during the follow-up period.

A total of 27 (26.4%) IBD patients had researched the relationship between IBD and COVID-19 on the internet during the pandemic, and 12 (44.4%) of them had sufficient information, while 10 (37.0%) patients had insufficient information, and 5 (18.5%) patients were unstable. No significant difference was noted between those who did research on the internet and those who did not in terms of the state of perceiving IBD disease as a risk for COVID-19 ($p>0.05$). However, the rate of those who did research on the internet, the perception that their drug usage could increase their risk to COVID was significantly higher when compared to those who did not research ($p=0.006$). In addition, 96 (94.1%) of the patients requested regular visits by phone during the pandemic period, and 95 of them (93.1%) stated that they thought it would be beneficial.

During the pandemic, 97 (95.08%) of the IBD patients without COVID-19 were questioned in terms of the most common symptoms of COVID-19 infection, and there were 67 (69.7%) patients who shared at least one of the symptoms. The most common symptoms were diarrhea (29.03%) and abdominal pain (20.64%). On excluding these most common symptoms of IBD during the re-evaluation, the next most common symptoms were sore throat, weakness, and cough (Table 4).

During the pandemic, COVID-19 infection was observed in 5 (4.90%) patients, including 4 patients with UC (pancolitis, n=3; distal type, n=1) and one patient with CD (colonic). Of these patients, 3 (60.0%) reported irregular drug use. Only one patient experienced an exacerbation during the pandemic period, but did not go to the hospital for the same. The other 4 patients showed no signs of exacerbation of IBD disease during the COVID-19 infection period. None of the patients had a history of cortisone use and endoscopic procedures during the pandemic. Two patients were using infliximab, one patient was using infliximab + azathiopurine, and two patients were using mesalazine. Infliximab and azathiopurine treatments were interrupted during the infection period, and 2 patients receiving mesalazine continued with their medications. Due to COVID-19 infection, 3 patients were followed up at the hospital and two patients at home. Two of the patients used plaquenil, another two patients used plaquenil, azithromycin, and oseltamivir, and one patient used a combination of plaquenil, azithromycin, oseltamivir, and favipravir. Intensive care admission and death were not reported for any of these patients. Infliximab and azathioprine were restarted after COVID-19 polymerase chain reaction tests turned negative. All of the patients requested phone visits during the pandemic and did not research their diseases on the internet. The most common symptom of these patients with COVID-19 infection was fatigue (80.0%).

DISCUSSION

IBD is a chronic inflammatory disease with exacerbation and remission periods. IBD patients perceive a risk of acquiring COVID-19 infection due to the usage of drugs such as immunosuppressants, immunomodulators, and anti-tumor necrosis factor (TNF) that could induce and maintain remission. In addition, it is an understandable condition that these patients are worried that the infection may progress to become more severe in the presence of COVID-19 infection (7). While the common GIS symptoms during COVID-19 infection are diarrhea, nausea, vomiting, abdominal pain, and anorexia, an exacerbation of IBD disease can be

Table 2. The perception of risk of patients for COVID-19

	Thinking the disease increases the risk of COVID-19, n (%)			Thinking drugs increase the risk of COVID-19, n (%)		
	Yes	No	No idea	Yes	No	No idea
UC (n=62)	36 (58.1)	20 (32.3)	6 (9.7)	8 (12.9)	44 (71.0)	10 (16.1)
CD (n=40)	18 (45.0)	11 (27.5)	11 (27.5)	7 (17.5)	19 (47.5)	14 (35.0)
IBD (n=102)	54 (52.9)	31 (30.3)	17 (16.6)	15 (14.7)	63 (61.7)	24 (23.5)

CD: Crohn's disease, UC: Ulcerative colitis, IBD: Inflammatory bowel disease, COVID-19: Coronavirus Disease-2019

triggered during this course, which may further complicate the condition (1).

It is difficult to distinguish between the symptoms of GIS such as diarrhea, abdominal pain, nausea, and vomiting, which are common in IBD patients, due to IBD exacerbations or because they overlap with those of COVID-19 infection. In our study, when IBD patients without COVID-19 were questioned in terms of the common symptoms in COVID-19 infection, abdominal pain and diarrhea were the most common responses. Less rectal bleeding in COVID-19 patients is important in clinical history. While patients with COVID-19 may have leukopenia (especially lymphopenia) and thrombocytopenia, patients with IBD exacerbation can usually be distinguished by having normal lymphocyte and leukocyte values and normal or increased platelet values (8,9). Diarrhea lasting for >4 weeks often suggests IBD-related colitis (10). In addition, the presence of symptoms such as cough, dyspnea, myalgia, contact with SARS-CoV-2-positive patients, or a travel history from areas considered to be at high risk for COVID-19 infection in the past 14 days are also considered important for the differential diagnosis of COVID-19 infection (11,12).

Table 3. Disease exacerbation and hospitalization status of IBD patients

	n (%)
Disease exacerbation in the last 3 months	
Yes	24 (23.5)
No	78 (76.5)
Going to the hospital after an exacerbation	
Yes	10 (41.7)
No	14 (58.3)
The reason for having a disease exacerbation and not going to the hospital	
Fear of risk of contracting COVID-19	9 (64.2)
Not being able to make an appointment	3 (21.4)
Other	2 (14.3)
Symptom onset and duration of hospitalization	
At once	4 (40)
Within 1 week	3 (30)
Within 2-3 weeks	3 (30)
After 3 weeks	0 (0)

IBD: Inflammatory bowel disease, COVID-19: Coronavirus Disease-2019

Table 4. Symptom distribution of IBD patients without COVID-19 infection

Symptom type	Number of responses, n	Total response, %
Diarrhea	45	29.0
Abdominal pain	32	20.6
Throat ache	22	14.1
Cough	16	10.3
Disappointment	16	10.3
Fire	12	7.7
Respiratory distress	6	3.8
Myalgia	3	1.9
Vomiting	3	1.9
Headache	0	0.0
Taste-odor disorder	0	0.0
Total	155	100

IBD: Inflammatory bowel disease, COVID-19: Coronavirus Disease-2019

In more than half of the patients with COVID-19-induced pneumonia, stool samples have been shown to be positive for SARS-CoV-2 and the stool samples of one-fifth of all infected patients were positive for SARS-CoV-2 despite having negative respiratory samples (13,14). Since inflammation in the intestines of IBD patients may increase the ACE2 expression, it can be assumed that patients with active IBD are an increased risk of SARS-CoV-2 infection. Although the delivery of SARS-CoV-2 occurs mainly through respiratory droplets, the ACE2 content is extremely low in the lungs than in other human tissues. This observation suggests that SARS-CoV-2 infection requires other not yet identified co-receptors or other additional factors than the ACE2 expression (15). In a study conducted for this purpose, IBD-associated inflammation alone was found to not fully meet the factors that allow the extra-respiratory passage of SARS-CoV-2 (16). In addition, cytokines documented in patients with severe COVID-19 and those observed during the "cytokine storm" syndrome (such as IL-2, IL-6, TNF, and interferon) are similar to cytokines released from the inflamed intestine of patients with IBD. There are a few publications that report the use of medical therapies to suppress inflammation in IBD as a beneficial step to prevent pneumonia due to COVID-19 while reducing the ongoing mucosal inflammation (17-19). In our study, the frequency of COVID-19 infection among the followed-up IBD patients was found to be 4.9%, none of which required intensive care and no mortality was reported. Four of these patients were receiving anti-TNF-based therapy.

Despite the presence of IBD being perceived as a potential risk for SARS-CoV-2, the limited available data and expert opinions suggest that IBD patients are not at an increased risk of SARS-CoV-2 infection (20). However, in our study, more than half of the patients believed that their disease posed a risk for COVID-19 infection rather than their medications, and the most common

drugs used by the patients who thought their drug usage was a risk factor was mesalazine. However, meselazines have very poor immunosuppressive effects and its long-term review is good safety side-effect profiles (21). The recommendations suggest that patients using mesalazine are at an increased risk to COVID-19 and hence their treatment should not be interrupted even during the active phase of the infection (22). In this regard, the use of both visual and written bulletins for IBD patients, addressing their concerns about the risks of drugs and their management should be well resolved.

During the pandemic, the use of regular medication is extremely important. Irregular drug use can cause severe disease flares, which may increase the need for additional treatment and endoscopic procedures. Considering that the primary priority of healthcare workers during the pandemic is COVID-19 and that they do not have spare time for IBD patients, it is recommended to not make changes in their medical treatments and to retain their current treatment regimens (23). In our study, approximately one-third of the patients using irregular medication experienced disease exacerbation and more than half of them could not go to the hospital due to the fear of infection or not getting an appointment. More than half of these patients who could go to the hospital were able to do so within 1-3 weeks of registering their complaints. This observation emphasizes the importance of the use of regular medications by patients during the pandemic.

The IBD population is generally composed of young patients. The relatively low prevalence of diseases such as diabetes, hypertension, and heart disease in this age group, which is associated with poor prognosis for COVID-19 infection, may explain the low comorbidity of COVID-19 infection despite that it is a chronic disease (24). Similarly, the mean age of the patients in the current study was 40.87±13.81 years.

The frequency of COVID-19 was lower in patients treated with anti-TNF-α than in those who received steroids. It has been reported that only a few IBD patients with COVID-19 infection required hospitalization when treated with anti-TNF-α when compared to those who received the steroid therapy (25). COVID-19 infection was not observed among patients using steroids who were followed up. This could be due to the fact that, during the pandemic, patients with steroid treatment were informed about the risks related to infection and recommended with the general precautions; moreover, these patients were followed up via teleconference from home to avoid their traveling to the hospital as much as possible during the steroid treatment. As in our study, the International Organization for the Study of IBD reported that telemedicine should be a fundamental part of patient management during the pandemic for IBD care, and this method is both cheaper and patient-oriented (26).

As is already known, during the pandemic, the general recommendations are that patients receiving treatment with anti-TNF-α and conical steroids should not discontinue their treatment if possible or, if the treatment has been planned but not started, other alternatives should be considered (27). In our study, in line with these recommendations, the received treatments by patients were not changed. Anti-TNF and azathioprine were suspended during the active COVID-19 infection period in IBD patients with COVID-19 treated with anti-TNF-α only, and the treatment was restarted when the test came negative.

In a survey of IBD patients by Chen et al. (28), the respondents reported that they were concerned about the risk of infection and access to healthcare, and only a quarter of them remained in telemedicine communication with their follow-up doctors for IBD. In our study, more than half of the patients who experienced disease exacerbation for IBD did not go to the hospital for the fear of infection. In addition, 96 (94.1%) of the patients requested regular visits via phone during the pandemic. It will thus be better to heed to these requests of the patients and design patient management plan accordingly in the following process.

CONCLUSION

Patients with IBD are those with chronic diseases that require immunosuppressive therapy. These patients should pay attention to the recommendations of the patient-based risk assessment of the prescribed drugs by the centers where they are followed so as to maintain the patients in their current treatment as much as possible and to take general protective measures to prevent infection. The majority of IBD patients with comorbidity should be treated and followed up via teleconference before requiring their visit to the hospital.

Action plans should be implemented in case of active IBD disease or COVID-19 infection. In addition, since this process is extremely dynamic, action plans supported by updated guidelines in the later stages of the pandemic will facilitate both physicians and patients to manage the process in an extremely healthy manner.

Ethics

Ethics Committee Approval: This study was approved by the Prof. Dr. Cemil Taşçıoğlu City Hospital/Local Human Research Ethics Committee, and all procedures conducted in the study involving human participants were in accordance with the ethical

standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Local Ethics Committee (12/05/2020 decision no: 156).

Informed Consent: All subjects included in this study agreed to their participation with their informed consent for the processing and collection of data for scientific purposes.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.G., Design: S.A., Data Collection or Processing: M.A., Analysis or Interpretation: N.E., Literature Search: Y.G., N.E., Writing: N.E., H.S.

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Comparison of the Diagnostic Accuracy of the Gamma-Glutamyl-Transpeptidase/Platelet Ratio with Aspartate Aminotransferase-Platelet Ratio Index and Fibrosis-4 Index in Liver Fibrosis in Chronic Hepatitis B

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Abstract

Objective: The gamma-glutamyl transpeptidase/platelet ratio (GPR) is a newly developed non-invasive serum marker of significant fibrosis and cirrhosis in patients with chronic hepatitis B (CHB) in West Africa. This study aimed to compare the diagnostic accuracy of the GPR with the aspartate aminotransferase-platelet ratio index (APRI) and with the fibrosis-4 (FIB-4) index for detecting liver fibrosis in Turkish patients with CHB.

Methods: Seventy-nine patients with CHB who had undergone liver biopsy were included, and GPR, APRI, and FIB-4 data were obtained. The receiver operating characteristic (ROC) curves and area under the ROC curves (AUROCs) were compared.

Results: As regards the fibrosis stages of 79 patients, 5 were F0 (6.3%), 17 were F1 (21.5%), 23 were F2 (29.1%), 23 were F3 (29.1%), and 11 were F4 (13.9%). The AUROCs of the GPR and APRI were similar in the diagnosis of significant fibrosis (0.70 vs. 0.69; p=0.928), advanced fibrosis (0.80 vs. 0.72; p=0.174), and cirrhosis (0.73 vs. 0.75; p=0.771) groups. The AUROCs of the GPR and FIB-4 index were similar for diagnosing significant fibrosis (0.70 vs. 0.79; p=0.090) and advanced fibrosis (0.80 vs. 0.77; p=0.569). However, the AUROCs of the FIB-4 index for diagnosing cirrhosis was significantly higher than those for the GPR (0.73 vs. 0.90; p=0.024) and APRI (0.75 vs. 0.90; p=0.024).

Conclusion: The GPR can be used to detect significant fibrosis, advanced fibrosis, and cirrhosis, but was not superior to the APRI or FIB-4 index. FIB-4 index performed better than the GPR and APRI for diagnosing cirrhosis.

Keywords: Gamma-glutamyl transpeptidase to platelet ratio, APRI, FIB-4, hepatic fibrosis, chronic hepatitis B

INTRODUCTION

Infection with hepatitis B virus (HBV) is an important health problem worldwide. According to the data of the World Health Organization (WHO), approximately 257 million people have chronic hepatitis B (CHB) infection (1). CHB is associated with an increased risk of cirrhosis and hepatocellular carcinoma (2). Early diagnosis and treatment are important in controlling disease progression and in reducing morbidity and mortality (3). The gold standard for the diagnosis of liver fibrosis is liver biopsy. However, its invasiveness, risk of complications, and contraindications, as well as patient discomfort, have limited its widespread use. It also has poor repeatability and sampling variability (4). Transient elastography (FibroScan) is a good alternative tool for diagnosing hepatic fibrosis because of its non-invasiveness, repeatability, and effectiveness. However, the FibroScan device (and annual maintenance thereof) is expensive

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and unavailable in many hospitals in Turkey. Additionally, the performance of FibroScan is compromised by many factors, such as ascites and obesity (5). Early detection of hepatic fibrosis with a simple, inexpensive, and non-invasive index in patients is important for timely treatment. Therefore, several serum marker panels, such as the aspartate aminotransferase (AST)-platelet ratio index (APRI) and fibrosis-4 (FIB-4) score, have been extensively investigated to detect liver fibrosis (6,7). The WHO has recommended an APRI score >2 to determine the presence of cirrhosis in adult patients with CHB, when resources are limited (8). However, the sensitivity and accuracy of the APRI and FIB-4 index in detecting HBV-associated fibrosis are only moderate (6). Lemoine et al. (9) developed the gamma-glutamyl transpeptidase (GGT)/platelet ratio (GPR) to predict liver fibrosis in West African patients with CHB and showed that GPR is superior to APRI and FIB-4 in detecting hepatic fibrosis. GPR performed better than APRI and FIB-4 index in a Chinese cohort (5), but such was not observed in patients with CHB in France nor in two other Chinese cohorts (9-11). Thus, further evaluation of the GPR in other cohorts is needed.

In this study, we investigated the diagnostic value of the GPR for liver fibrosis and cirrhosis in Turkish patients with CHB. This study thus aimed to compare the performance of the GPR, APRI, and FIB-4 index for diagnosing significant fibrosis and cirrhosis in patients with CHB.

METHODS

Data of 91 patients with CHB who underwent liver biopsy between January 2017 and March 2020 in the gastroenterology department of the University of Health Sciences Gaziosmanpasa Hospital were retrospectively analyzed. However, patients with insufficient clinical data, with high GGT values due to excess alcohol consumption or obesity, and with hepatitis D were excluded; thus, the remaining 79 patients were included in the study. Liver biopsies of patients with CHB were taken prior to the start of the antiviral therapy. The diagnosis of CHB infection was determined by positive hepatitis B surface antigen for at least 6 months (12). Medical records of the patients and laboratory measurements such as AST, alanine transaminase, GGT, platelet count, HBV deoxyribonucleic acid (DNA) levels, and HBV serological markers were recorded retrospectively.

The degree of hepatic fibrosis was noted in all patients. Histologically, liver fibrosis was classified according to the METAVIR scoring system (13): F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with several septa; F3, multiple septa without cirrhosis; and F4, cirrhosis. In addition, significant fibrosis was identified as ≥F2, advanced fibrosis as ≥F3, and cirrhosis as F4.

This study protocol was approved by the Ethics Committee of Gaziosmanpaşa Training and Research Hospital (no: 189, date: 18.11.2020) and conformed with the Declaration of Helsinki. All patients were enrolled after they provided informed consent.

The formulas for the GPR, APRI, and FIB-4 index are shown below:

1- GPR=[GGT (IU/L)/upper limit of normal (ULN) of GGT]/platelet count (10^9/L) x100

2) APRI=[AST (IU/L)/ULN of AST)]/platelet count (10^9/L) x100

3) FIB-4 index=[age (years) x AST (IU/L)]/(platelet count (10^9/L) x [ALT (IU/L)$^{1/2}$]

Note: ULN of AST=35 IU/L; ULN of GGT=38 IU/L.

Statistical Analysis

SPSS 22.0 software for Windows (IBM Corp., Armonk, NY, USA) was used for the analyses. The normality of the distributions of the numerical variables was tested with the Shapiro-Wilk test. The Mann-Whitney U test was used to compare variables that were not normally distributed between two independent groups, and Kruskal-Wallis and Dunn tests were used to compare more than two groups. The relationship between the numerical variables was tested with Spearman's rank correlation coefficient analysis. A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off points of the variables in the fibrosis groups. The area under the ROC curves (AUROCs) for significant fibrosis (≥ F2), advanced fibrosis (≥ F3), and cirrhosis (F4), were obtained by comparing F2-F4 patients with F0-F1 patients, F3-F4 patients with F0-F2 patients, and F4 patients with F0-F3 patients, respectively. A p value <0.05 was considered significant.

RESULTS

Baseline Patient Characteristics

The baseline characteristics of the patients are presented in Table 1. A total of 79 patients [male, 48 (60.8%); female, 31 (39.2%)] participated in this study. The average age of the patients was 44.11±13.65 years. There were 60 (75.9%) patients negative for hepatitis B e-antigen (HBeAg) and 19 (24.1%) patients positive for HBeAg. The distribution of patients according to their fibrosis stages is as follows: F0, n=5 (6.3%); F1, n=17 (21.5%); F2, n=23 (29.1%); F3, n=23 (29.1%); and F4, n=11 (13.9%). The median (interquartile range) HBV DNA level was 67,000 (20,900-

14,384,997) IU/L, the AST level was 36.6 (25.0, 52.0) IU/L, the ALT level was 50.0 (26.0, 84.0) IU/L, the GGT level was 25.0 (16.0, 44.0) IU/L, and the platelet count was 207 (170, 242) x10^9/L. The median GPR, APRI, and FIB-4 index values were 0.32 (0.19, 0.64), 0.39 (0.23, 0.55), and 0.96 (0.66, 1.70), respectively.

Correlations of the GPR, APRI, and FIB-4 Index with Liver Fibrosis Stage

Relationships between serum models and liver fibrosis stages were evaluated using Spearman's correlation analysis. A positive correlation was detected between the liver fibrosis score and the GPR (r=0.470, p<0.01), APRI (r=0.354, p<0.01), and FIB-4 index (r=0.565, p<0.01). The highest correlation coefficient was seen between the fibrosis and FIB-4 index.

The GPR (p=0.001), APRI (p=0.003), FIB-4 index (p=0.001), and GGT (p=0.001) value were significantly higher in patients with significant fibrosis (F ≥2) than in those without fibrosis. GPR, APRI, and FIB-4 index values increased with fibrosis stages in patients with CHB (Table 2).

Table 1. Baseline patient characteristics

	Patients (n=79)
Age (y), mean (SD)	44.11 (13.65)
Male sex, n (%)	48 (60.8)
HBV DNA (IU/mL), median (IQR)	67000 (20,900-14,384,997)
AST (IU/L), median (IQR)	36.6 (25.0-52.0)
ALT (IU/L), median (IQR)	50.0 (26.0-84.0)
GGT (IU/L), median (IQR)	25.0 (16.0-44.0)
Platelet (10^9/L), median (IQR)	207 (170-242)
Fibrosis stages n (%)	
F0	5 (6.3%)
F1	17 (21.5%)
F2	23 (29.1%)
F3	23 (29.1%)
F4	11 (13.9%)
GPR, median (IQR)	0.32 (0.19-0.64)
APRI, median (IQR)	0.39 (0.23-0.55)
FIB-4, median (IQR)	0.96 (0.66-1.70)

IQR: Interquartile range, HBV: Hepatitis B virus, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl-transpeptidase, GPR: Gamma-glutamyl-transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4, SD: Standard deviation

Diagnostic Performance of the GPR, APRI, and FIB-4 for Liver Fibrosis and Cirrhosis

The AUROCs of the serum models for cirrhosis and liver fibrosis are shown in Table 3. The AUROCs of the GPR and APRI were comparable for significant fibrosis (0.70 vs. 0.69; p=0.928), advanced fibrosis (0.80 vs. 0.72; p=0.174), and cirrhosis (0.73 vs. 0.75; p=0.771). The AUROCs of the GPR and FIB-4 index were comparable for diagnosing significant fibrosis (0.70 vs. 0.79; p=0.090) and advanced fibrosis (0.80 vs. 0.77; p=0.569); however, the AUROC of the FIB-4 index for diagnosing cirrhosis was significantly higher than that of the GPR (0.73 vs. 0.90; p=0.024). Similarly, the AUROC of the FIB-4 index was higher than that of the APRI in predicting cirrhosis (0.75 vs. 0.90; p=0.024). The ROC curves of the GPR, APRI, and FIB-4 index for diagnosing significant fibrosis, advanced fibrosis, and cirrhosis are shown in Figure 1.

DISCUSSION

In this study, we measured the accuracy of the GPR to non-invasively diagnose hepatic fibrosis, using the gold standard (liver biopsy) as a reference. The AUROC values of the GPR for significant fibrosis, advanced fibrosis, and cirrhosis in patients

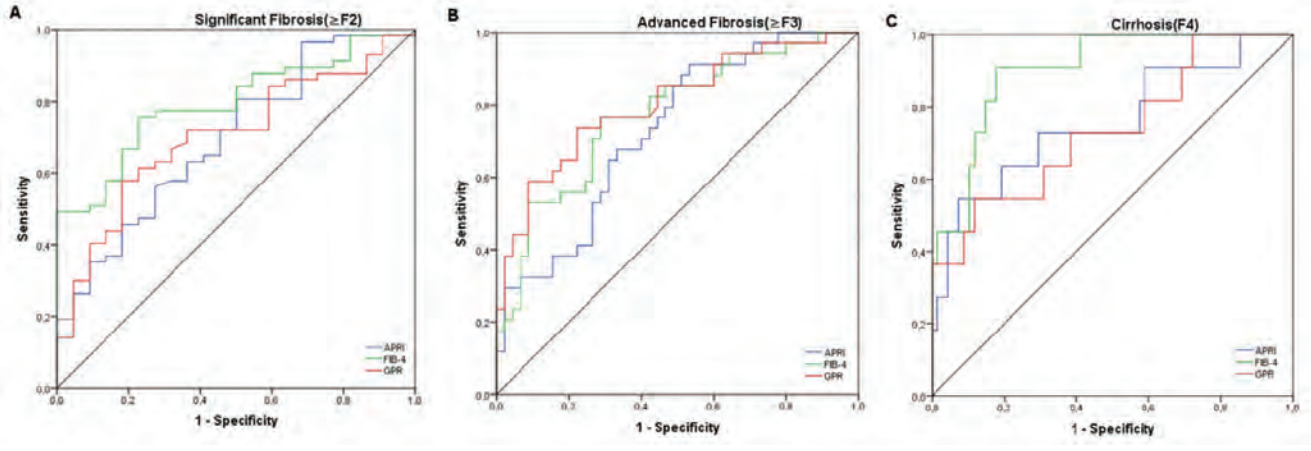

Figure 1. ROC curves of the GPR, APRI, and FIB-4 index for diagnosing significant fibrosis (A), advanced fibrosis (B), and cirrhosis (C).
ROC: Receiver operating characteristic, GPR: Gamma-glutamyl transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4

with CHB were 0.70, 0.80, and 0.73, respectively. In addition, a positive correlation was found between the GPR and fibrosis stage. However, the GPR was not superior to the APRI or FIB-4 index in determining significant fibrosis, advanced fibrosis, or cirrhosis in our Turkish patients with CHB.

Continuous monitoring of fibrosis, which causes mortality and morbidity in patients with CHB, is important for prognosis and informing treatment decisions (14). Serum models have been developed as an alternative to liver biopsy in determining the severity of a liver disease (10). Increased GGT activity has recently been reported as an important marker of liver damage and fibrosis progression (15). In addition, a negative correlation has been observed between significant fibrosis and platelet count (16). Lemoine et al. (9) developed the GPR as a new marker of the degree of hepatic fibrosis based on the GGT and platelet count. Studies have compared the performance of the GPR with the APRI and FIB-4 index for diagnosing hepatic fibrosis, but the results have been inconsistent. A study has suggested that GPR is superior to APRI and FIB-4 index for diagnosing significant fibrosis and cirrhosis in Gambia and Senegal cohorts, while GPR is not superior to APRI or FIB-4 index for evaluating hepatic fibrosis in a French cohort (9). Li et al. (11) evaluated the diagnostic value of the GPR in a retrospective study in China that included 372 patients with CHB and demonstrated that the GPR was not superior to the APRI or FIB-4 index for determining hepatic fibrosis. The performance of the GPR, APRI, and FIB-4 index was comparable for diagnosing hepatic fibrosis in another Chinese cohort (10). However, Hu et al. (5) showed that the AUROC values of GPRs were more accurate than those of APRI and FIB-4 index with respect to the degree of liver fibrosis.

In our study, the AUROC values of GPR for significant fibrosis and cirrhosis (0.70 and 0.73, respectively) were lower than those obtained by Lemoine et al. (9) (0.80 and 0.83, respectively), while the AUROC values for advanced fibrosis were similar between the two studies (0.80 and 0.81, respectively). Moreover, the GPR values correlated with the degree of hepatic fibrosis. According to these results, the GPR had acceptable performance for detecting liver fibrosis in our study population (p=0.001). However, the performance of the GPR in diagnosing liver fibrosis was not better than that of APRI or FIB-4 index. The AUROC values of APRI were 0.69, 0.72, and 0.75, and those of FIB-4 index were 0.79, 0.77, and 0.90, for significant fibrosis, advanced fibrosis, and cirrhosis, respectively. FIB-4 could be a better serum marker of cirrhosis than the GPR (AUROC: 0.90 and 0.73, respectively; p=0.024) and APRI (AUROC: 0.90 and 0.75,

Table 2. Serum markers by liver fibrosis stage

	Fibrosis stages				
Serum markers	**F0-F1**	**F2**	**F3**	**F4**	**p values**
GPR	0.23 (0.16-0.34)	0.30 (0.18-0.43)	0.54 (0.29-0.76)	0.80 (0.35-1.74)	0.001*
APRI	0.28 (0.17-0.45)	0.37 (0.19-0.59)	0.40 (0.26-0.49)	0.85 (0.38-1.09)	0.003*
FIB-4	0.71 (0.55-0.81)	0.94 (0.70-1.78)	1.21 (0.71-1.77)	2.39 (1.73-3.55)	0.001*
GGT	21.00 (15.00-29.50)	19.50 (14.00-28.00)	42.00 (23.00-65.00)	37.50 (19.50-87.50)	0.001*

Median (IQR) *p<0.05, IQR: Interquartile range, GGT: Gamma-glutamyl-transpeptidase, GPR: Gamma-glutamyl-transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4

Table 3. Diagnostic performance of serum markers for liver fibrosis and cirrhosis

	Significant fibrosis			Advanced fibrosis			Cirrhosis		
	≥ F2 (F0-F1 vs. F2-F4)			≥ F3 (F0-F2 vs. F3-F4)			F4 (F0-F3 vs. F4)		
	GPR	**APRI**	**FIB-4**	**GPR**	**APRI**	**FIB-4**	**GPR**	**APRI**	**FIB-4**
AUROC	0.703	0.697	0.794	0.802	0.727	0.771	0.737	0.757	0.902
95% CI	0.59-0.80	0.58-0.79	0.69-0.88	0.70-0.88	0.61-0.82	0.66-0.86	0.62-0.83	0.65-0.85	0.81-0.96
Cut-off value	0.35	0.24	0.81	0.36	0.26	0.96	0.72	0.74	1.41
Sensitivity	57.89	80.70	75.44	73.53	91.18	76.47	54.55	54.55	90.91
Specificity	81.82	50.00	77.27	77.78	46.67	71.11	88.24	92.65	82.35
PPV, %	42.85	50.00	53.33	79.07	87.50	80.00	92.30	92.64	98.24
NPV, %	89.19	80.70	87.75	69.44	56.36	66.66	42.85	54.54	45.45

AUROC: Area under the receiver operating characteristic curve, PPV: Positive predictive value, NPV: Negative predictive value, GPR: Gamma-glutamyl-transpeptidase to platelet ratio index, APRI: Aspartate transaminase to platelet ratio index, FIB-4: Fibrosis-4, CI: Confidence interval

respectively; p=0.024). The cut-off value of the FIB-4 index for diagnosing cirrhosis was 1.41, with 90% sensitivity and 82.5% specificity. Teshale et al. (17) reported high AUROC values for APRI and FIB-4 index in the diagnosis of liver fibrosis in patients with CHB, and high specificity and sensitivity for APRI and FIB-4 in distinguishing F2-F4 from F0-F1. However, some Chinese studies have reported that GPR has a higher AUROC value for the diagnosis of significant fibrosis and cirrhosis in patients with CHB (5,18). Lemoine et al. (9) observed poor performance of the APRI and FIB-4 index for detecting significant fibrosis and cirrhosis.

One possible reason for the inconsistent results is related to the differences in interregional HBV genotypes. According to epidemiological evidence, genotype A is common in Africa and Europe and genotypes B and C in Asia (19). As genotype D is the most common HBV genotype in the Mediterranean region, we assumed that this HBV genotype is also common in Turkey (20).

Study Limitations

Patient selection bias cannot be ruled out, primarily because this was a single-center study conducted in a tertiary referral center, in which patients with significant and advanced fibrosis are more prevalent than the general patient population. Moreover, the sample size of our study (especially the number of patients with cirrhosis) was relatively small. In addition, data were obtained retrospectively, and no dynamic GPR measurements were taken.

CONCLUSION

The GPR showed acceptable diagnostic performance for significant fibrosis, advanced fibrosis, and cirrhosis, but was not superior to the APRI or FIB-4 index. The correlations with fibrosis stage were similar among the GPR, APRI, and FIB-4 index. The FIB-4 index showed better diagnostic performance for cirrhosis than the GPR and APRI. Further large-scale studies are needed to confirm these results.

Ethics

Ethics Committee Approval: This study protocol was approved by the Ethics Committee of Gaziosmanpasa Training and Research Hospital (no: 189, date: 18.11.2020) and conformed with the Declaration of Helsinki.

Informed Consent: All patients were enrolled after they provided informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Ö.K., Y.G., Design: D.Ö.K., Y.G., Data Collection or Processing: D.Ö.K., Y.G., Analysis or Interpretation: D.Ö.K., Y.G., Literature Search: D.Ö.K., Y.G., Writing: D.Ö.K., Y.G.

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CASE REPORT

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Lymphoepithelioma of Larynx: Case Report

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Abstract

Lymphoepithelial carcinoma (LEC) refers to a non-keratinized undifferentiated type of nasopharyngeal carcinoma. It rarely originates from the larynx mucosa. A 73-year-old male patient with a long term history of snoking was admitted to the hospital with a one-year history of dyspnea, dysphagia and dysphonia. Laryngeal LEC diagnosis was confirmed by a laryngeal biopsy. We presented a case report of locally advanced LEC of the larynx with only radiotherapy treatment.

Keywords: Lymphoepithelioma, larynx, radiotherapy

INTRODUCTION

Lymphoepithelial carcinoma (LEC) is a term used for neoplasms associated with non-keratinized undifferentiated nasopharyngeal carcinoma (WHO type 3). LEC is rarely caused by nasopharynx in the head and neck mucosa. It is characterized by the presence of lobules, sheets, nests and lymphoplasmacytic cell stroma which separates cords of neoplastic cells. It may also be associated with Epstein-Barr virus (EBV). Our report is a case of locally advanced LEC treated with radiotherapy.

CASE PRESENTATION

A 73-year-old male with a long term history of smoking applied with complaints of dysphagia, dysphonia and dyspnea for over a year, was admitted to our hospital with respiratory distress and hypoxia. Laryngoscopic examination of the patient revealed a supraglottic larynx mass.

It was a partially ulcerated lesion on the left aryepiglottic fold extending to the left ventricle (Figure 1a, b). The head and neck examinations revealed no palpable neck masses. Nasopharyngoscopy was used to detect the nasopharyngeal mass. Tracheostomy was opened to the patient. Nasopharyngeal and laryngeal biopsy was performed. A computerized tomography scan of the neck revealed a supraglottic mass measuring 37x30 mm in size, extending over the vocal cord, aryepiglottic fold and piriform sinus (malignancy). The lesion invaded the arytenoid cartilage and extended into the paralaryngeal area and fat planes (Figure 2a, b).

Nasopharynx biopsy resulted in reactive lymphoid hyperplasia microscopic analysis, and immunohistochemistry of laryngeal biopsy confirmed the diagnosis of laryngeal LEC (Figure 3). There were significant nucleolus tumor cells with large vesicle nuclei (Figure 3a), and vesicular nucleoli with prominent nucleoli tumor cells between lymphoid cells (Figure 3b). The pan-cytokeratin staining (Figure 3c) was seen among tumor cells, CD3 positive lymphoid cells (Figure 3d) and CD20 positive lymphoid cells (Figure 3e). EBV RNA (EBER) was negative in the case. Radiotherapy was applied to our patient. The whole larynx area received 30 cures of 60 Gray radiotherapy. The tumor area was given 3 cures of 66 Gray radiotherapies. After 18 months of follow up recurrence or metastases was detected. The consent was obtained from patient.

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DISCUSSION

LEC is characterized by primitive, undifferentiated, non-keratinized epithelial cells interpresed with non-neoplastic lymphocytes. LEC is reported in different parts of the head and neck mucosa like a sinonasal tract, salivary gland especially parotid gland, larynx and hypopharynx. LEC have been reported in the larynx rarely.

LEC constitutes 0.2% of all laryngeal cancers in men, mainly in elderly patients (1).

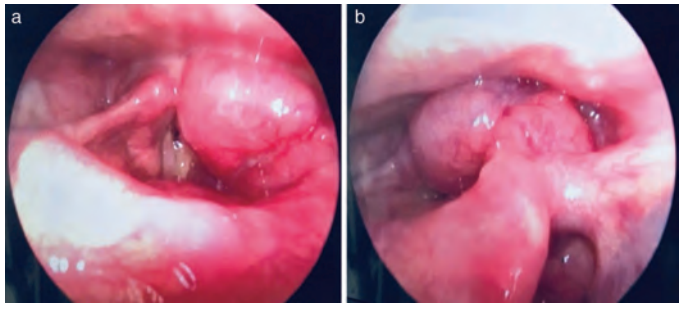

Figure 1a, b. Mass occupying supraglottic levels of the larynx. On endoscopic examination, a partially ulcerated lesion of the left aryepiglottic fold extending to the left ventricle

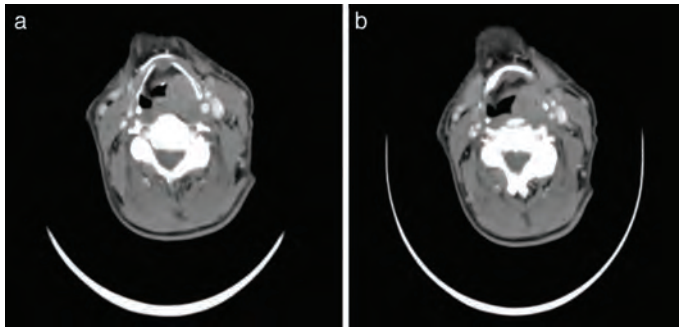

Figure 2a, b. Computed tomography scanning of the mass

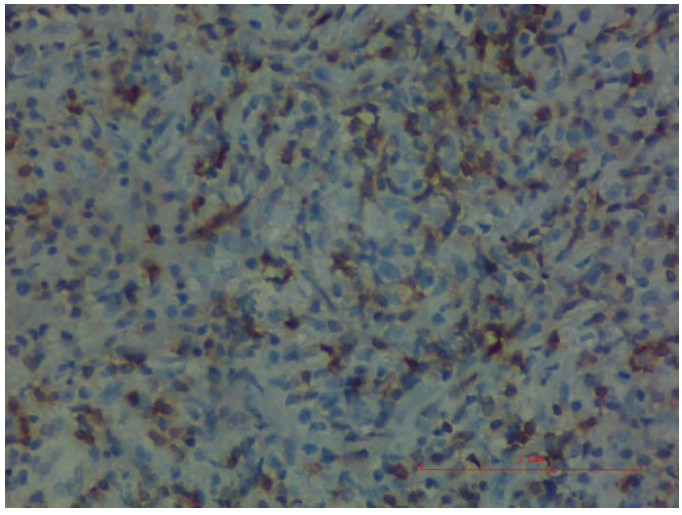

Figure 3a. Significant nucleolus tumor cells with large vesicle nuclei

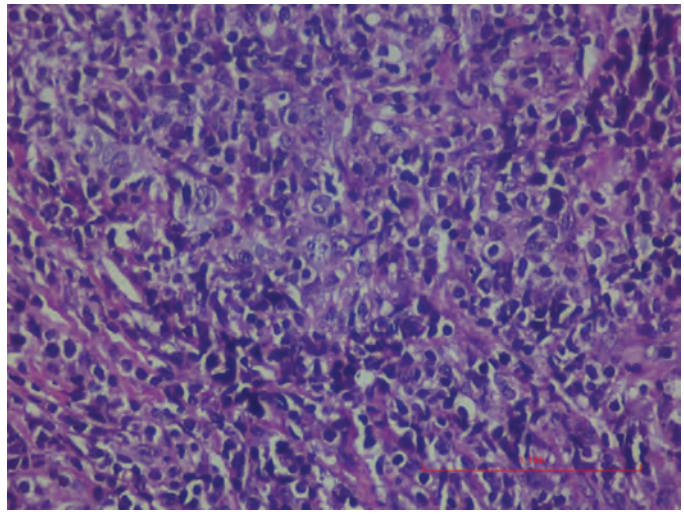

Figure 3b. Between lymphoid cells, vesicular nucleoli with prominent nucleoli tumor cells

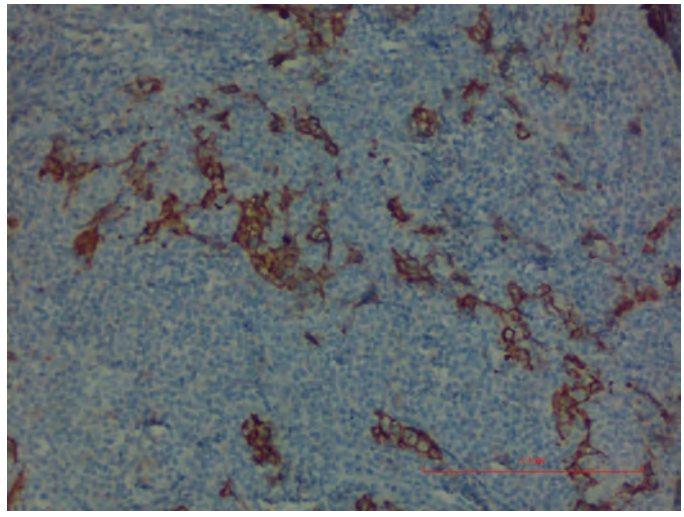

Figure 3c. Pan-cytokeratin staining

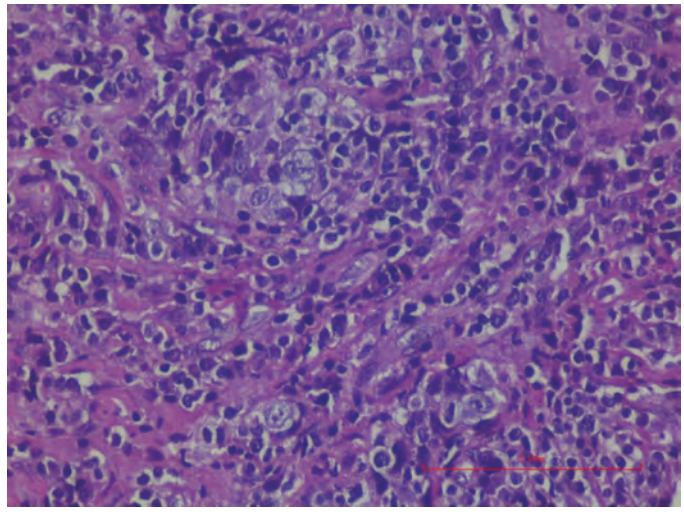

Figure 3d. Among tumor cells, CD3 positive lymphoid cells

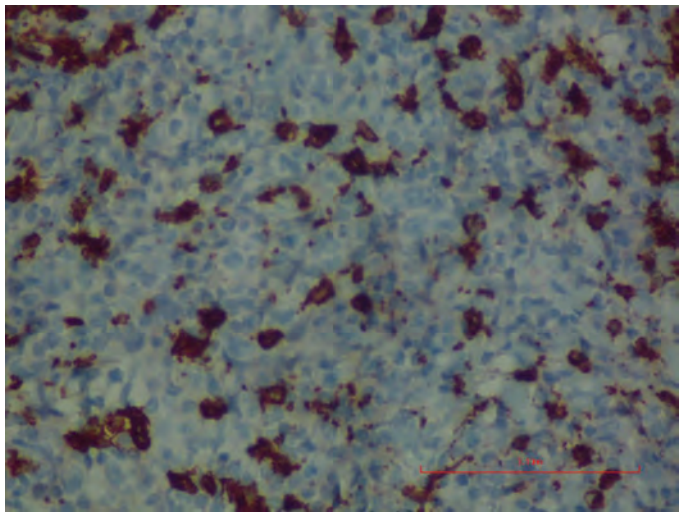

Figure 3e. Among tumor cells, CD20 positive lymphoid cells

Laryngeal LEC is considered to be similar to nasopharyngeal lenfoepithlioma except for its localization. Like nasopharyngeal carcinoma, LEC is also strongly associated with heavy cigarette smoking (2-5). In this case the patient also was a heavy smoker.

EBV antigens can be shown in immunohistochemical and molecular species. Macmillan et al. (5) reported no EBV involvement in their eight cases series but P53 expression was positive. Some authors declare that in endemic regions, EBER can be positive and can be used for diagnosis (5-7). Marioni et al. (8) published that EBV plays a limited role in the etiology of LEC of the larynx. In their study reviewed in the report of the 34 cases of LEC, only 16 were evaluated for the presence of EBV and it was demonstrated in only four cases (25%). In our case, EBER was determined negative.

There is no special place for LEC but supraglottic localization is more prevalent (9), Micheau et al. (10). In a total of 1350 laryngeal surgical specimens, three are LEC cases in the larynx. Among the three cases, the LEC epiglottis was found on the laryngeal surface and was associated with the laryngocele in two cases. Toker and Peterson (11) reported a case of LEC of the larynx which had a peculiar property of tonsillar epithelium and might have been its origin. In our case, the lesion was in the supraglottic location and extended to the vocal band and ventricle. The mass was causing obstruction of the airway and emergent tracheostomy was performed. There was no case reported which required emergent tracheotomy in the literature.

Histopathologically, LEC is characterized by poorly differentiated, non-keratinized cells with large, round, vesicular nuclei, each containing a single large usually centrally located, basophilic to the deep red prominent nucleolus. Immunohistochemical staining is positive for keratin and epithelial membrane antigen. Differential diagnosis should be made by immunohistochemical methods in the positive cytokeratin menu for the identification of the malicious squamous component (4-6). Dysphonia, dysphagia, dyspnea and otalgia are the major symptoms. Lymphadenopathy can be encountered as well (2). In our case dysphonia and dyspnea were the main symptoms. There was no cervical lymph node encountered. Cervical lymph node metastasis was reported in the literature approximately 75% (5,7,8).

The distant distance metastasis rate is also high. Metastasis was not seen in this case (12).

Treatment of LEC is mostly radiotherapy or surgery with radiotherapy combination (7,13). Laryngeal LEC is a highly radiosensitive disease and excellent local control rates can be achieved with radiotherapy (2). No comparative studies have been done, therefore, organ-preserving treatment methods are preferred. In our case, the patient received radioterapy after 18 months of follow up. No recurrence or metastases were detected.

CONCLUSION

Early detection is important and essential to distinguish the LEC from squamous cell carcinoma. The role of EBV is still not clear, and EBER can be used for differential diagnosis.

Radiotherapy which is the only treatment for local disease is recommended. Chemotherapy may also play a role in patients with advanced disease as well as in those with lymph node invasion.

Ethics

Informed Consent: The consent was obtained from patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.T., G.B., Y.U., Design: F.A., Y.U., Data Collection or Processing: Z.S., Analysis or Interpretation: B.T., P.Ö.N., Literature Search: F.A., Writing: B.T., İ.A.A.

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

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CASE REPORT

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Extracapsular Hip Fracture Management of a Patient Infected with COVID-19: A Novel Case Report

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Abstract

The timing surgical treatment of a hip fracture on a patient with Coronavirus Disease-2019 (COVID-19) related pneumonia is determined based on the general condition of the patient and the circumstance of active disease in the lung. The common rule of earlier surgery is better motto, which is valid under normal conditions, can be stretched during the pandemic period, especially if the patient is infected with COVID-19. However, about the timing of surgery, attention should be paid to the patient's active lung infection condition in order to prevent facilitating the spread of the virus in the lung during intubation.

Keywords: COVID-19, SARS-CoV-2, intubation, intertrochanteric femur fracture, hip fracture, timing of surgery

INTRODUCTION

Coronaviridae virus family member Severe Acute Respiratory syndrome (SARS), also known as Coronavirus Disease-2019 (COVID-19), is a pandemic outbreak. Viruses of the family have a single-strand, positive-sense RNA genome, ranging from 26 to 32 kilobases in length (1). Among several coronaviruses pathogenic to humans, most are associated with mild clinical symptoms, with two notable exceptions: (a) SARS-coronavirus-2 (SARS-CoV-2), which is a novel beta coronavirus that emerged in Guangdong, southern China, in November 2002, and resulted in more than 8,000 human infections and 774 deaths in 37 countries from 2002 to 2003, and (b) the Middle East Respiratory Syndrome-CoV-2, which was first detected in Saudi Arabia in 2012 and was responsible for 2,494 laboratory-confirmed infection cases and 858 fatalities since September 2012 (2-4). In late December 2019, several patients with viral pneumonia were epidemiologically associated with the Huanan seafood market in Wuhan, in China's Hubei province, where several nonaquatic animals such as birds and rabbits were for sale before the outbreak. A novel, human-infecting coronavirus, provisionally named 2019 novel coronavirus, was identified using next-generation sequencing (4-7). On March 11, 2020, the first case of the coronavirus pandemic was seen in Turkey according to the Turkish Ministry of Health. As time passed, the number of cases has dramatically increased in Turkey, which eventually declared an epidemic, and in many other countries. On the other hand, hip fractures are common among elderly adults, and these are generally related to osteoporosis. The two main types of hip fractures are femoral neck and intertrochanteric region proximal femoral fractures. Transtrochanteric femur fractures are usually common in older patients and are related to femoral neck fractures. However, patients infected with SARS-CoV-2 can experience concomitant health problems. In this case, a patient was infected with coronavirus, which was incidentally found in the hospital while being referred to the orthopedic clinic by the emergency department because of intertrochanteric region proximal femur fracture.

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CASE PRESENTATION

A 70-year-old male patient was admitted to the emergency department with a complaint of left hip pain after a fall. His wife was also admitted with symptoms of dyspnea and high fever. The coronavirus outbreak affects large areas, and every patient in the risk group who is admitted to our emergency room is assumed to be infected with SARS-CoV-2. Therefore, emergency service doctors have examined the patient and requested a thorax computed tomography (CT) scan for both our patient and his wife. The husband was referred to the orthopedic outpatient clinic from our emergency service with suspected left hip fracture.

Results from the CT scan revealed left extracapsular proximal femoral fracture and a chest finding that was suggestive of SARS-CoV-2 infection (Figure 1). An urinary catheter was inserted, and above-the-knee surgical stockings were applied on both legs to prevent embolization and urinary retention. He had no diagnosed morbidity but had a history of plastic surgery for a basal cell carcinoma in the facial region 6 years ago. We placed the patient in a temporary trauma observation room in our emergency department. Treatment was started immediately with subcutaneous enoxaparin sodium 60 mg twice a day (equivalent to 6000 anti-Xa molecules each), 0.9% sodium chloride infusion at 100 mL/h daily, intravenous omeprazole 40 mg once a day, and intravenous paracetamol 1000 mg four times a day (8). Moreover, intravenous tramadol 100 mg was added to his daily treatment chart and can be given as needed up to three times a day. The treatment regimen continued until discharge. Furthermore, the patient received respiratory physiotherapy three times a day for at least 10 min in the clinic.

Immobilization in elderly can cause severe problems such as delirium, venous embolization, electrolyte imbalances, urinary tract infection, depression, and muscle atrophy. Hence, urgent fixation surgery and rapid mobilization after surgery are required for elderly with hip fractures. During regular schedules, our orthopedic and trauma clinic performs hip fracture surgery in elderly patients on the day after admission or 48 h subsequent to admission at maximum.

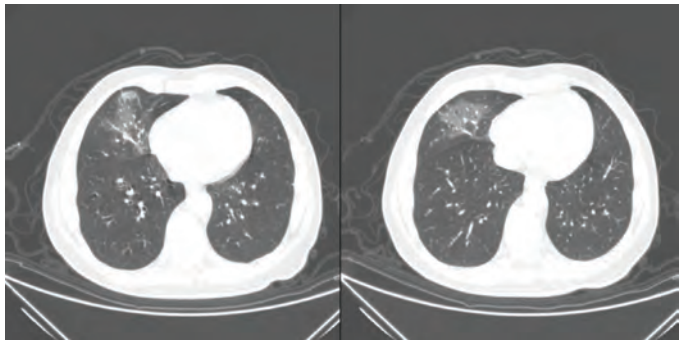

Figure 1. Thorax computed tomography of the patient on the day of admission

Generally, we admit patients in the hospital after checking their full blood count and giving their first medical treatment doses. However, in this case, the patient was first referred to the infectious diseases clinic because of suspicious thorax CT scan signs and pulmonary examination. In addition, the patient also had an uncertain contact history with SARS-CoV-2 infected people.

An infectious diseases and clinical microbiology consultant evaluated the patient, and a suspected SARS-CoV-2 related pneumonia was unveiled. After hospital admission, the infectious diseases and clinical microbiology requested again for surgical procedure availability and further suggestions. Consulting specialists recommended a few days' rest before surgery for the lungs to stabilize and infection to recede because of the high risk of intubation and mechanical ventilation, which will worsen the pneumonia. In our hospital, spinal anesthesia is used for hip fractures. However, the anesthesiology department did not want to risk as they did not have the option to shift to general anesthesia as consultations from the infectious diseases and clinical microbiology and pulmonology revealed that his lung condition can worsen after intubation and mechanical ventilation. Thus, the surgery was postponed.

In our hospital, patients infected with SARS-CoV-2 are placed in special isolation rooms. The patient and his wife were placed in the same isolation room; both were assumed to be SARS-CoV-2 positive. Both patients had thorax CT scans highly compatible with SARS-CoV-2 related pneumonia. Nasopharyngeal swab samples were instantly collected for real-time polymerase chain reaction (PCR) tests at hospitalization. On admission, the patient had a 37.0 °C temperature, 84 beats per minute heart rate, 166/100 blood pressure, and 97% oxygen saturation on room air. Oral hydroxychloroquine sulfate for 5 days (initial dose of oral 400 mg twice a day peroral on the first day, then maintenance dose 200 mg twice a day peroral 4 days) and intravenous ceftriaxone 1 g three times a day for 7 days for pneumonia and oral clarithromycin 500 mg twice a day for 7 days for infection were added in the treatment chart. All doses of oral hydroxychloroquine were taken with a glass of milk. Therapy for SARS-CoV-2 pneumonia proceeded relentlessly, and anticoagulants, pain killers, proton pump inhibitors, and physiotherapy were continued. On the third day, the patient's PCR test came out negative, but his wife had a positive PCR test result. So, the treatment remained unaltered (9).

During the entire hospitalization period, temperature, heart rate, respiration rate, and peripheral blood oxygen saturation were checked every hour. Daily electrocardiogram was done and QT interval calculated. Cognitive status was checked every day using the Memorial Delirium Assessment scale: no dysdiadochokinesia, no dyskinesia, no delirium, and no agitation were seen (10). The patient had a perpetual cough on the first two days and high fever (38.6 °C) on the first day. Daily urinary output and liquid intake, including 2,400 mL intravenous solution of 0.9% sodium chloride, were recorded. Balanced total liquid intake and output were targeted. Besides, full blood count and blood biochemistry were checked daily to prevent hyperchloremic metabolic acidosis.

Consequently, minimal side effects were seen. Headaches were present on the first two days, but he had no diarrhea or rigid constipation. Even so, we advised a fibrous-weighted diet.

After the treatment was completed, approval for surgery was granted by both clinical microbiology and infectious diseases and pulmonology specialists. Thus, the patient went for surgery the day after. Informed consent was taken from the patient the day before operation; both the patient and his family were given detailed information about the procedure and possible complications.

There is a controversial debate on the gold standard treatment of extracapsular proximal femoral fractures. In our clinic, we prefer to perform intramedullary hip screw fixation for all AO 31-A type fractures (11), and this was done in this patient (Figures 2 and 3).

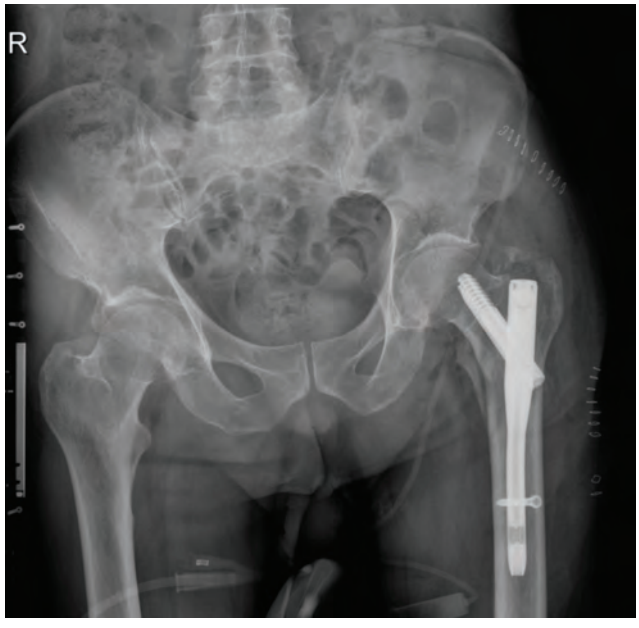

Figure 2. Anteroposterior radiograph of the patient's pelvis at first day postoperation

During surgery, each surgical staff wore a surgical mask as a cover of filtering facepiece class 3 mask and donned a transparent face shield on top. Moreover, they wore two pairs of sterile surgical apron and a lead apron on the innermost to shield them from the C-arm image intensifier radiation. At the bottom, all staff members wore rain boots, which are used only in surgery. Following the advice of the Turkish Ministry of Health, the A-M-G-H abbreviation was followed as a sequence for donning personal protective equipment: aprons, masks, glasses or face shields, and gloves.

The surgery lasted for 1 h and 15 min, from skin incision to bandage. The image intensifier was used during the surgery. Although the surgical team was prompt, it took them longer than usual to take perioperative image intensifier shots. The operating team was composed of two surgeons (one orthopedic consultant and one fourth-year orthopedic resident), one surgical nurse, one anesthesiology technician, one anesthesiology consultant, and one operation room janitor. The aim was to perform the surgical procedure with maximal productivity and minimal complication.

A day after surgery, the patient started to mobilize with supervision from the orthopedic physiotherapist. Whole weight-bearing mobilization was performed. Vitamin D, calcium, and zinc supplements were started for support. Discharge planning was difficult because of the recent surgery, but the patient's C-reactive protein and leukocyte count were controlled, and his subsequent thorax CT showed relevant healing results (Figure 4).

Consequently, the patient was informed about the rehabilitation process and given detailed instructions about beneficial actions for recovery. The patient and his family were informed about this study before discharge, and informed consent was obtained. Eventually, our patient was discharged from the hospital on the 15th day after his isolation period. Unfortunately, the patient's

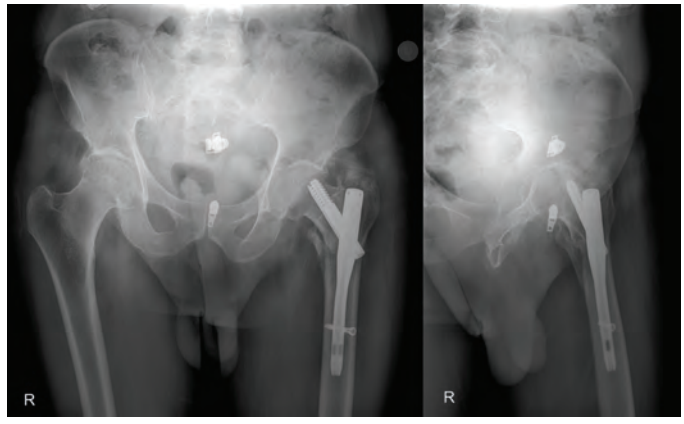

Figure 3. Pelvis anteroposterior and L-femur lateral radiographs of the patient at postoperative 6 weeks

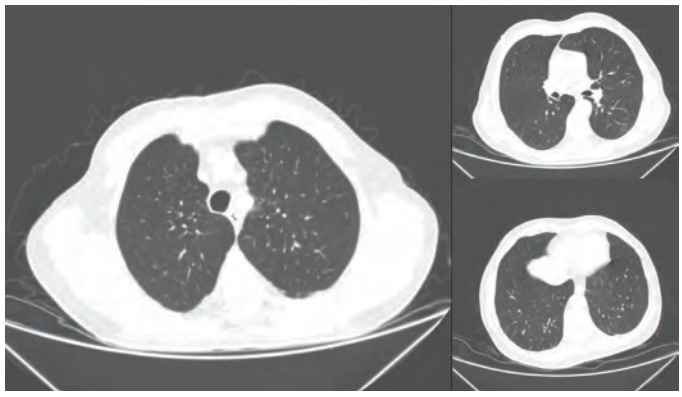

Figure 4. Patient's thorax computed tomography scans on the 14th day of hospitalization

wife died in the intensive care unit because of acute respiratory distress syndrome due to SARS-CoV-2.

DISCUSSION

Many published articles on hip fractures in elderly people stated that early surgical treatment in the first 24 h is beneficial to reduce the rate of perioperative complications and mortality (12).

However, circumstances are not always appropriate for early surgery (13). These inconvenient conditions are sometimes due to the patient's general health or, in the current times, to the hospital's conditions. In this case study, the patient initially presented with a highly contagious pandemic viral infection SARS-CoV-2. The patient had viral pneumonia, and his respiratory system and vitals were strictly observed. After treating pneumonia, the patient was operated for hip fracture under firm precautions for healthcare workers. Although our patient was admitted together with his wife, he seemed to be luckier than her as he was discharged from the hospital after 15 days. The Turkey Ministry of Health demands an isolation period of 14 days for individuals infected or suspected of SARS-CoV-2. Thus, the patient has completed the isolation period.

To conclude, an outweighed conservative orthopedic treatment is preferred in these pandemic days (14). A surgical procedure performed as soon as possible and short hospitalization period are preferred to minimize contagious risks (12).

In managing trauma patients infected with SARS-CoV2, precautious treatment protocols are in place to preserve the well-being of both patients and healthcare workers. For us, the aim is to rapidly operate elderly with hip fractures; however, in our opinion, delaying surgery does not affect mortality if the patient has a condition that needs to be resolved preoperatively (15).

CONCLUSION

Finally, as we reported in this case, we consider that delaying surgery for selected trauma patients infected with SARS-CoV2 is the best option.

Ethics

Informed Consent: Informed consent was taken from the patient the day before operation.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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

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INTERESTING IMAGE

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Total Aortic Occlusion: A Rare Cause of Paraplegia

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Abstract

Total aortic occlusion is a rare disease and may lead to catastrophic outcomes. Although it can be acute or subacute, mortality or morbidity is high if early intervention is not performed. In this report, we described the case of a 90-year-old female patient with total aortic occlusion who presented to the emergency department with paraplegia.

Keywords: Aortic occlusion, paraplegia, totally

INTRODUCTION

A 90-year-old female patient presented to our emergency department with a sudden onset of inability to walk, leg numbness, and back pain. She has no history other than ischemic heart disease. On admission, she had blood pressure of 200/90 mmHg, pulse rate of 86 beats per minute, and respiration rate of 16 breaths per minute. On physical examination, peripheral pulses could not be obtained; bilateral lower extremities were pale and cold; and she had muscle strength of 1/5. Aortoperipheral contrast-enhanced computed tomography (CT) angiography showed total aortic occlusion in the infrarenal region, including the iliac arteries.

Informed consent was obtained from the patient for the publication of this case report.

Total Aortic Occlusion

Total aortic occlusion is a rare disease and may lead to catastrophic outcomes. Although it can be acute or subacute, mortality or morbidity is high if early intervention is not performed. "Leriche syndrome" is defined as total aortic occlusion presented to the emergency department with the absence of lower extremity pulse, erectile dysfunction, and loss of sensation (1). The gold standard for diagnosis is contrast-enhanced CT angiography. Our patient was admitted to the emergency department with low back pain and inability to walk. Pulse examination prevented misdiagnosis. Tissue hypoxia was the cause of the low back pain and leg pain. The main reason for the inability to walk is the occlusion of the vertebral arteries (2). In particular, patients presenting with low back pain can often be overlooked in the emergency department. Therefore, for aortic occlusion, appropriate and careful examination of patients with low back pain and paraplegia is important.

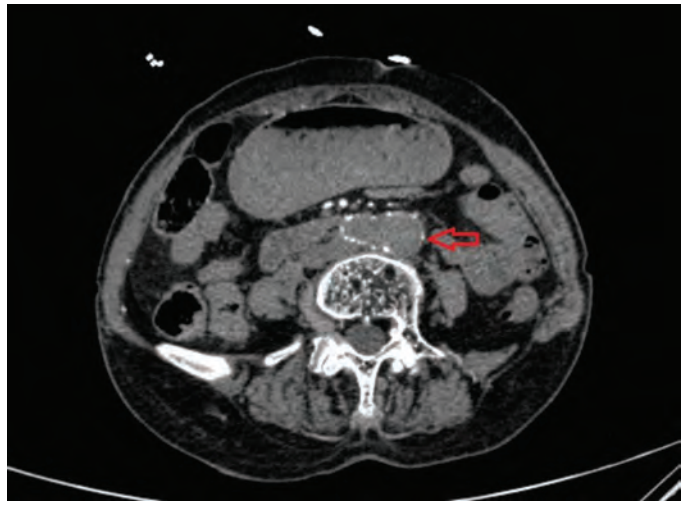

Figure 1. Total aortic occlusion at the infrarenal level (transverse)

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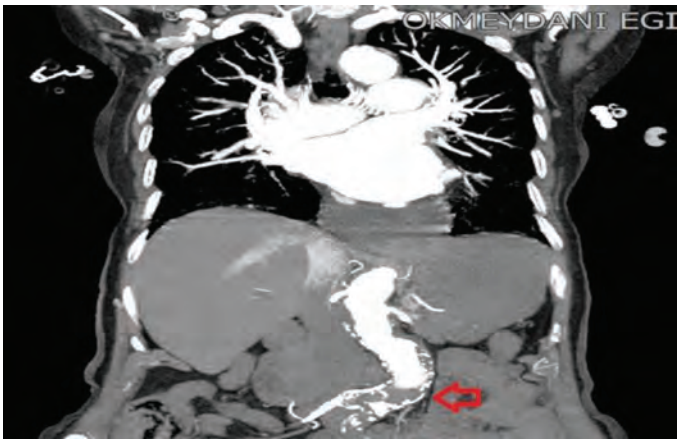

Figure 2. Total aortic occlusion at the infrarenal level (sagittal)

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.K., E.M.B., Design: M.Ş., Data Collection or Processing: E.M.B., M.Ş., Analysis or Interpretation: A.K., M.E.F., E.M.B., Literature Search: E.M.B., M.E.F., M.Ş., Writing: A.K., M.Ş., M.E.F.

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

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