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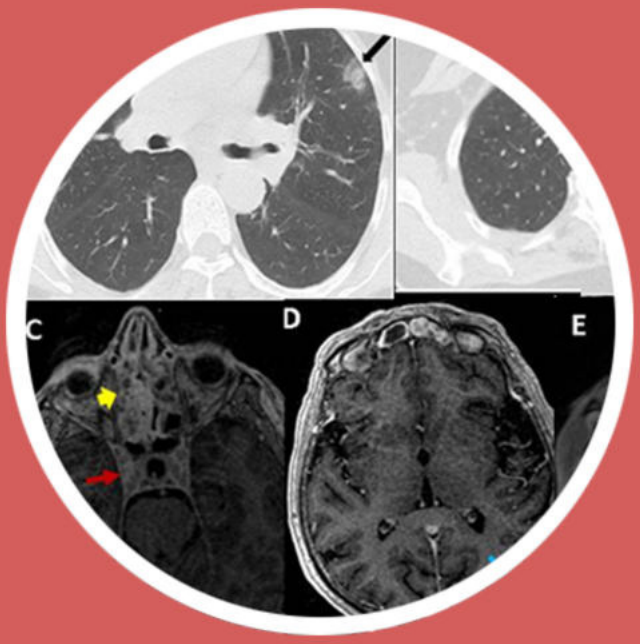

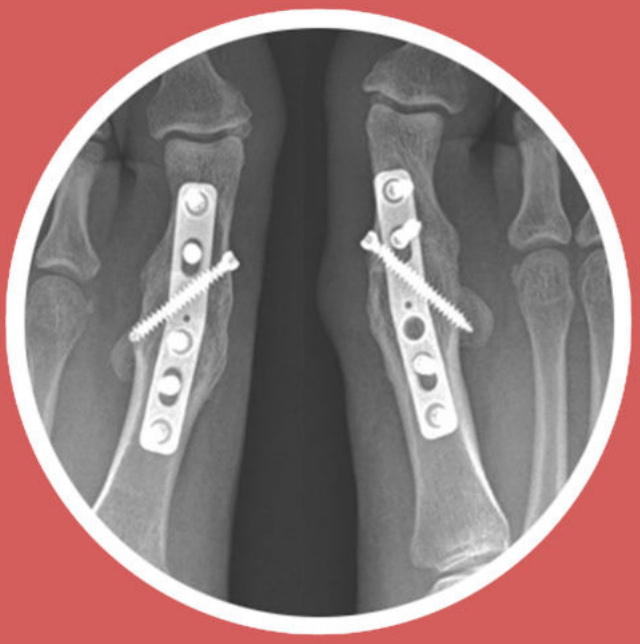

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The European Research Journal 2022;8(1):1-8 Original Article

DOI: 10.18621/eurj.817200 *Orthopaedics and Traumatology*

A retrospective investigation of the effect of tranexamic acid application and tourniquet duration on postoperative bleeding amount in patients undergoing total knee arthroplasty

Mustafa Onur Karaca, Abdullah Merter, Kerem Başarır, Mehmet Bahaddin Güzel

Department of Orthopaedics and Traumatology, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objectives: It is aimed to investigate the effect of tourniquet and tranexamic acid (TXA) on the amount of perioperative bleeding in patients undergoing total knee arthroplasty.

Methods: One hundred and ninety-three patients included in the study. The patients included in the study were divided into 4 groups. Group 1 (n = 78) was determined as the patient group with long-term tourniquet application, but without additional application and was accepted as the control group. Group 2 (n = 40) was the long-term tourniquet and intravenous (IV) TXA applied group, Group 3 (n = 40) was the long-term tourniquet and intra-articular TXA applied group, and Group 4 (n = 35) was the short-term tourniquet (only in the cementing phase) and IV TXA applied group. The difference between groups according to use of a tourniquet during the operation, the method and dose of TXA, the amount of postoperative blood transfusion, the amount of drained blood, the length of hospital stay, and complications were investigated.

Results: The largest Hemoglobin (Hb) and Hematocrit (Hct) decreases were found in Group 1 (3.39 ± 0.92 g/dl and 10.8%, respectively). Also the highest drainage (median 350 ml), transfusion (16.7%), length of hospital stay (mean 4.51 ± 1.07 days) and estimated blood loss (median 1559.8 ml) were in Group 1 ($p < 0.05$). The lowest Hb decrease (mean 2.95 ± 0.68 g/dl) and lowest drainage (median 150 ml) was seen in group 3 and the lowest length of hospital stay (mean 3.89 ± 0.8 days) in group 4 ($p < 0.05$).

Conclusions: The use of TXA was shown to lead to a reduction in Hb and Hct, the amount of blood drained after surgery, and the length of hospital stay. The use of TXA may be a good option for bleeding control in patients undergoing total knee arthroplasty.

Keywords: Tranexamic acid, arthroplasty, tourniquets, drains

Total knee arthroplasty is among the current treatment options for advanced-stage gonarthrosis [1-3]. In the literature, it has been reported that the average amount of bleeding in total knee arthroplasty operations is between 800-1800 ml [4, 5]. Blood transfusion applied due to bleeding prolongs both the rehabilitation period and the length of hospital stay [6]. It also causes severe complications such as transfusion reaction, infection, metabolite imbalances, hemolysis, and immune system inhibition [7-9].

In total knee arthroplasty, a tourniquet is used to avoid complications related to blood transfusion. Stud-

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ies have shown that bleeding is less in cases where a tourniquet was used during total knee arthroplasty [2, 3]. However, it has also been shown that tourniquet use has complications such as quadriceps weakness, postoperative hip pain, local inflammation, and muscle damage [10-12]. Therefore, short-term use of a tourniquet (at the cementing stage) has been examined. Postoperative pain, swelling, and limitation of movement are less common in patients in whom short-term tourniquets are applied [10, 13-16].

Due to the complications seen in the use of a tourniquet, the use of antifibrinolytic agents has been given prominence in recent years to reduce bleeding [17, 18]. Tranexamic acid (TXA) is one of these agents. It shows antifibrinolytic activity by inactivating plasminogen [19]. Tranexamic acid can be administered in a number of different ways (oral, intravenous, intra-articular). Although there are studies showing that each method is effective in reducing bleeding, which method and which dose are most effective in patients with total knee arthroplasty remain controversial [1, 6].

The present study aims to investigate the effect of tourniquet and TXA on the amount of perioperative bleeding in patients undergoing total knee arthroplasty, in addition to which, the efficacy difference between intravenous and intraarticular administrations of TXA is evaluated.

METHODS

In the university hospital where the study was conducted, a total of 245 cases of patients, who had undergone total knee arthroplasty between May 2014 and June 2015, were retrospectively scanned from the hospital archives. Patients with anemia (< 12 g/L for females, < 13 g/L for males) (n = 10), comorbid disease (kidney dysfunction, cardiovascular disease, cerebrovascular disease, thromboembolic disease) (n = 9), body mass index (BMI) > 50 kg/m^2 (n = 7), tranexamic acid allergy (TXA) (n = 1), advanced deformity before surgery (flexion deformity > 30^o, varus and/or valgus deformity > 30^o) (n = 12), and bilateral total knee arthroplasty (n = 13) were excluded from the study.

The information of 193 patients included in the study such as age, gender, side, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) category, preoperative and postoperative hemoglobin (Hb), hematocrit (Hct) values, etiology of osteoarthrosis (osteoarthritis, rheumatoid arthritis, post-traumatic arthritis or osteonecrosis) was obtained from the hospital registry system. The use of a tourniquet during the operation, the method and dose of TXA, the amount of postoperative blood transfusion, the amount of drained blood, the length of hospital stay, and complications were also reviewed in the hospital registry system.

All patients were operated in the same clinic by two surgeons using the same surgical method. In the group of patients in grouop 1, 2 and 4, the tourniquet was inflated just before the incision to 100 mm Hg, more than the systemic systolic blood pressure of the patient. The tourniquet was deflated immediately after the incision was closed. In group 3, the tourniquet was inflated before the application of cement and removed just before the wound was closed when the cement had hardened. Intravenous (IV) TXA application was performed just before the incision with 10-15 mg/kg in 100 cc saline solution, and intra-articular application was performed by applying 2 g TXA into the joint after the capsule was closed. None of the patients received TXA after surgery. Electrocautery was used for bleeding control, but no other local chemical agents were used. While the knee was in the 90^o flexion position and the incision was being closed, subcutaneous suturing was applied with a monofilament suture material, with a topical skin adhesive (Dermabond; Ethicon) then used. In all cases, drains were routinely applied. In patients undergoing intra-articular TXA, the drain was clamped for two hours. All patients were treated with 3×1 g IV cefazolin sodium until the drain was removed after surgery. Celecoxib, ketorolac (max 2 doses), hydrocodone and acetaminophen were used for pain control and tramadol after surgery. Quadriceps strengthening, active and passive range of motion and walking exercises began on the first day after surgery. Hb and Hct control were performed on all patients undergoing arthroplasty on day 0, day 1, and day 3. Blood transfusion was applied to patients who were Hb < 7 g/dl or Hb < 8 g/dl and symptomatic.

The patients included in the study were divided into 4 groups according to the tourniquet duration and TXA administration method. Group 1 (n = 78) was determined as the patient group with long-term tourni-

quet application, but without additional application and was accepted as the control group. Group 2 (n = 40) was the long-term tourniquet and IV TXA application just before the incision with 10-15 mg/kg in 100 cc saline solution, Group 3 (n = 40) was the long-term tourniquet and intra-articular 2 g TXA into the joint after the capsule was closed group, and Group 4 (n = 35) was the short-term tourniquet (only in the cementing phase) and IV TXA application just before the incision with 10-15 mg/kg in 100 cc saline solution.

All reported research involving "Human beings" conducted in accordance with the principles set forth in the Helsinki Declaration 2008. This study was carried out with the permission of the ethics committee of the hospital where it was conducted dated 16.06.2015; No. 10-420-15 of. The patients and/or their families were informed that data would be submitted for publication, and gave their consent.

Statistical Analysis

The analysis of the data was carried out using the SPSS for Windows 25 package program. Descriptive statistics were shown as mean ± standard deviation for variables with normal distribution, and median (min - max) for non-distributed variables, while nominal variables were expressed as number of cases and (%). While the variance analysis (ANOVA) test was used for the significance of the difference between the groups in terms of averages, the Fisher's Least Significant Difference (LSD) was used for the significance of the difference in terms of median values and the Dunn's Test was used for the post-hoc analysis. Nominal variables were evaluated by the Pearson Chi-Square test. The results were considered statistically significant for $p < 0.05$.

RESULTS

The mean age of 193 patients (163 females and 30 males) included in the study was 67.8 ± 7.9 years. One hundred and one patients were operated on the right knee and 92 patients on the left and the mean BMI of the patients was 31.1 ± 4.7 kg/m^2. Distribution of demographic data by groups and osteoarthritis etiologies are shown in Table 1. The brands and models of the

Table 1. Demographic characteristics of the patients

	Group 1 (n = 78)	Group 2 (n = 40)	Group 3 (n = 40)	Group 4 (n = 35)	*p* value
	Mean ± SD.	**Mean ± SD.**	**Mean ± SD.**	**Mean ± SD.**	
Age (years)	66.6 ± 7.8	66.9 ± 8.1	67.9 ± 6.1	71.1 ± 9.6	**0.047[a]**
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Sex					
Female	67 (85.9)	36 (90.0)	32 (80.0)	28 (80.0)	0.533[p]
Male	11 (14.1)	4 (10.0)	8 (20.0)	7 (20.0)	
Side					
Right	41 (52.6)	23 (57.5)	17 (42.5)	20 (57.1)	0.512[p]
Left	37 (47.4)	17 (42.5)	23 (57.5)	15 (42.9)	
	Median (Min-Max)	**Median (Min-Max**	**Median (Min-Max**	**Median (Min-Max**	
BMI	30.4 (20.7-44)	29.7 (22.7-48.2)	31.6 (25.3-44.9)	31.2 (21.7-48.4)	0.230[k]
Starting hemoglobin (g/dL)	13.2 (10.7-16.1)	13.6 (10.2-15.6)	13.2 (10.4-16.3)	13.6 (12.2-16.3)	0.201[k]
Starting hematocrit (g/dL)	39.9 (32.8-49.4)	40.8 (30.3-48.8)	39.7 (33.3-49.3)	40.4 (36.8-49)	0.518[k]

[a]OneWay ANOVA Test, Post Hoc Test = Fisher's Least Significant Difference (LSD), [p]Pearson chi-square test, [k]Kruskal-Wallis test, [S]Significance for Group 1, SD = Standard deviation, Min = Minimum, Max = Maximum, BMI = Body mass index

Table 2. Knee replacement systems

	Biomet Vanguard®	Depuy P.F.C. Sigma®	Exactech Optetrak®	Smith & Nephew Genesis II®	Biomet ROCC®
Group 1	22	19	25	11	1
Group 2	27	13	-	-	-
Group 3	24	8	-	4	4
Group 4	20	15	-	-	-

implants applied to the patients are shown in Table 2.

The largest Hb and Hct decreases were found in Group 1 (3.39 ± 0.92 g/dl and 10.8%, respectively). Similarly, the highest drainage (median 350 ml), transfusion (16.7%), length of hospital stay (mean 4.51 ± 1.07 days) and estimated blood loss (median 1559.8 ml) were in Group 1, and this difference was statistically significant ($p < 0.05$). The lowest Hb decrease (mean 2.95 ± 0.68 g/dl) and the lowest drainage was found in Group 3 (median 150 ml; range 50 to 500 ml), and the lowest length of hospital stay (mean 3.89 ± 0.8 days) in group 4. This difference was statistically significant ($p < 0.05$). The distribution of the evaluation criteria by groups and comparison of the groups with each other are shown in Table 3.

DISCUSSION

A tourniquet is routinely used by many surgeons in total knee arthroplasty surgery. The application of tranexamic acid has become increasingly popular in recent years [17, 18]. Many studies in the literature show that it reduces bleeding in arthroplasty surgeries. In a prospective randomized controlled study conducted by Huang *et al*. [2] with 150 patients in 2017, patients who received multiple doses of oral and IV TXA were found to have fewer instances of hidden blood loss, swelling and pain, and lower inflammatory markers compared to patients in whom only a tourniquet was applied. In a prospective randomized study by Santias *et al*. [20], 2 g TXA/50 ml topical admin-

Table 3. Comparison of differences in blood loss

	Max hb drop (g/dL)	Max htc drop (%)	Drained blood (ml)	Transfusions	Length of stay (days)	EVB calculated blood loss
	Mean ± SD	Median (Min-Max	Median (Min-Max)	n (%)	Mean ± SD	Median (Min-Max)
Group 1	3.39 ± 0.92	10.8 (4.1-17.8)	350 (20-1000)	13 (16.7%)	4.51 ± 1.07	1559.8 (468.6-3620.5)
Group 2	2.85 ± 0.99	8.6 (2.9-15)	285 (50-500)	3 (7.5%)	4.10 ± 0.9	1077.6 (393.2-2065.1)
Group 3	2.80 ± 0.67	8.9 (5.2-12.7)	150 (50-500)	4 (10%)	3.97 ± 0.7	1273.4 (614.5-2459.4)
Group 4	2.95 ± 0.68	8.8 (4.4-11.2)	225 (75-425)	2 (5.7%)	3.89 ± 0.8	1212.2 (638.2-2369.2)
***p* value**	**< 0.001[a]**	**< 0.001[k]**	**< 0.001[k]**	0.337[p]	**0.002[a]**	**< 0.001[k]**
G1-G2	**0.029**	**< 0.001**	**0.018**	ns	0.183	**< 0.001**
G1-G3	**0.009**	**< 0.001**	**< 0.001**	> 0.05	0.066	**0.009**
G1-G4	0.402	**< 0.001**	**< 0.001**	> 0.05	**0.008**	**0.001**
G2-G3	0.774	0.705	**0.001**	> 0.05	0.553	0.224
G2-G4	0.626	0.948	0.202	> 0.05	0.327	0.589
G3-G4	0.445	0.764	**0.049**	> 0.05	0.683	0.525

[a]One Way ANOVA Test, Post Hoc Test = Fisher's Least Significant Difference (LSD), [p]Pearson chi-square test, [k]Kruskal-Wallis test, Post Hoc Test = Dunn's Test, SD = Standard deviation, Min = Minimum, Max = Maximum, G = group, Hb =hemoglobin, Htc = hematocrit, Tq = tourniquet, iv = intravenous, ia = intraarticular, Group1 = Tourniquet only, Group2 = Tq and iv TXA, Group 3 = Tq and ia TXA), Group 4 = Tq cementing and iv TXA

istration has been shown to reduce the amount of postoperative bleeding without increasing thromboembolic risks in primary cemented total knee arthroplasty cases. Meng *et al*. [21] made an evaluation especially for an obese patient group, where it was difficult to use a tourniquet. They showed that the use of TXA reduced bleeding and concluded that obese patients benefit more from TXA than individuals of normal body weight [21]. In their study, which included 180 patients, Tzatzairis *et al*. showed that the administration of 3 doses of IV TXA significantly reduced allogeneic blood transfusion and blood loss in patients who underwent arthroplasty without tourniquet [22]. In the present study, less significant Hb and Hct reductions, and less drainage were found in the groups that underwent TXA (Group 2 and 3) compared to the group where only a tourniquet was applied (Group 1), and there was a statistically significant difference in all of these evaluation criteria. Unlike other studies in the literature, there was no patient group in this study where the tourniquet was not applied. Therefore, it is necessary to consider this difference when comparing it with other studies. In the present study, the use of TXA with tourniquets has been shown to reduce blood loss and drainage amount. A patient group (Group 4), in which the duration of the tourniquet application was limited, was also taken into consideration. Although there was a statistically significant difference between Group 4 and Group 1 in terms of the maximum Hct decrease and drainage amount, no difference was found between other groups. It was seen that long-term tourniquet use did not have a significant effect in terms of reducing bleeding compared to short-term use. However, it was found that tourniquet use of limited duration with TXA was more effective when compared to cases where TXA was not used.

In addition to the effective use of tranexamic acid, its form of application and dosage are also important [23]. In a compilation study published by Brusalis *et al*. [24] in 2018 in reference to the randomized controlled prospective study of Huang *et al*. [2], it was stated that for the use of TXA to be more effective and in order to increase its routine application, it is necessary to determine the optimum methods of administration and doses. In a meta-analysis conducted in 2017, patients, who underwent total hip and total knee arthroplasty, were evaluated. There was no difference between topical and IV TXA administration in terms of transfusion amount and safety. Given the maximum decrease in hemoglobin level, IV administration was shown to be more advantageous [25]. Oral TXA administration was also shown to be effective in a systematic compilation and meta-analysis involving 608 patients [26]. In a prospective randomized clinical study conducted in 2018, there was no difference between oral and IV administration in terms of Hb and Hct decrease, blood loss, inflammatory, and fibrinolytic response [27]. In another meta-analysis conducted in 2018, it was emphasized that there was no difference between oral administration and IV administration, and oral use might be preferred due to ease of administration and "cost-benefit superiority" [28]. In a randomized controlled study comparing intra-articular, intravenous, and combined administration, intra-articular, and IV-combined administration was shown to be more effective than other methods in reducing blood loss [29]. In the present study, there was no difference between the group where TXA was administered intraarticularly and the group where TXA was applied intravenously in terms of Hb and Hct decreases, while the amount of drained blood was significantly lower in the group where TXA was administered intraarticularly compared to the group where TXA was applied intravenously. The amount of drainage in the intra-articular group was found to be statistically significantly lower than all other groups. This situation can be interpreted as the use of local intraarticular tranexamic acid in the knee limiting the bleeding within the knee by forming a hematoma. This may cause clogging of the drain and less drainage compared to other groups. Also the hematoma-preventing properties of the drains used should be taken into consideration.

Discussions about the most appropriate dose as well as the preferred method of administration for TXA continue in the literature [23]. In a study conducted in 2016, a single preoperative dose of 30 mg/kg TXA (2.5g maximum) resulted in the need for less transfusion in patients with elective primary hip and knee arthroplasty compared to lower doses [22]. In a study by Tzatzairis *et al*. [22], administration of 15 mg/kg IV TXA with 3 doses (during induction, at the 3rd and 6th hour) was shown to be more effective than one or two doses. In a study conducted with 175 pa-

tients in 2019, in addition to the patients in the placebo group, there were those who were administered a preoperative single dose of IV 20 mg/kg, and those who received IV TXA for a total of six times (a total of 6 g maximum) within the first 24 hours after induction, with the least loss found to be in the six-dose group when these were evaluated in terms of latent blood loss [22]. A dose comparison was not intended in the present study. However, it was found that the best result in the study groups was to apply 2 g of TXA into the joint immediately after the joint capsule was closed.

In addition to the use of tranexamic acid, another issue is the duration of tourniquet use in total knee arthroplasty surgeries. There is no consensus in the literature on this subject. In a study by Li *et al*. [30], it was shown that different tourniquet durations did not create a difference in the amount of bleeding during surgery and the need for postoperative transfusion [30]. In another study published in 2020, it was found that short-term tourniquet use with TXA application led to a reduction in Hb and transfusion requirement, and these patients had less thigh pain and a shorter length of hospital stay compared to patients in whom a long-term tourniquet was applied.

Similarly, in the present study, there was a difference in the amount of bleeding only in the group of patients (Group 4), who had a tourniquet only during the cement application with IV TXA compared to the group that did not undergo TXA. However, no significant difference was seen between Group 2 and Group 4. Short term tourniquet application did not cause any further bleeding. Besides, it was seen that the duration of hospital stay was shortest in the patient group (Group 4) undergoing short-term tourniquet application. In conclusion, the present study shows that short-term tourniquet application together with TXA is an effective method. Studies to be conducted in large series and standard patient groups will be able to provide more precise information on this subject.

Limitations

This study has some limitations. The number of patients was limited due to the retrospective nature of the study and the breadth of the exclusion criteria used in order to facilitate standardization of the patient groups. Nevertheless, when the patients were divided into groups, the number of patients was found to be sufficient to make a statistically significant difference. However, multicenter studies in large series, will result in the availability of more comprehensive information. Since there was no patient group in which a tourniquet was not used in the current clinical practice, no such control group could be created. Different application methods were compared. However, different drug dose effects should be evaluated using the data in this study. The present study can serve as a basis for similar studies.

CONCLUSION

In conclusion, the use of TXA was shown to lead to a reduction in Hb and Hct, the amount of blood drained after surgery, and the length of hospital stay. The lowest Hb decrease was seen in the group where intra-articular TXA was applied and the lowest length of hospital stay in the group where the short-term tourniquet was applied. Prospective studies using different drug doses and larger series will provide clearer inferences in this regard.

Authors' Contribution

Study Conception: MOK, KB, MBG; Study Design: MOK, AM, KB; Supervision: MOK, AM, MBG; Funding: MOK, AM, MBG; Materials: MOK, KB, MBG; Data Collection and/or Processing: MOK, AM, KB; Statistical Analysis and/or Data Interpretation: MOK, AM, KB, MBG; Literature Review: MOK, AM, KB; Manuscript Preparation: MOK, AM, KB and Critical Review: MOK, AM, KB, MBG.

Ethical approval

Approval was obtained from the ethics committee of Ankara University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The paraoxonase 1 activity and lipid levels in umbilical cord blood and maternal venous blood, and their relations according to birth weight

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ABSTRACT

Objectives: Aim of this study is to find out the clinical relevance of estimating paraoxonase activity of PON1 enzyme, triglyceride (TG), total cholesterol, HDL, and LDL levels in maternal serum and umbilical cord blood according to birth weight.

Methods: Venous blood samples were taken from mothers just before birth. Babies were divided into four groups: normal-weight babies, premature babies, low birth weight babies, and postmature babies. The weight of the newborns was measured and cord blood was taken. The samples were looked at HDL, LDL, total cholesterol, triglyceride levels and PON1 activities. We have investigated the paraoxonase activity of the PON1 enzyme. Enzyme activity assay was obtained spectrophotometrically measurement of p−nitrophenol at 412 nm.

Results: Maternal PON1 paraoxonase activity levels in Pre-Term show a significant decrease in cases as compared to other groups. Baby PON1 paraoxonase activity levels are also found to be significantly decreased in cases concerning the Term and Post-Term groups. There was a significant difference in all values the such as baby's weight, TG, Total cholesterol, HDL, LDL and PON1.belonging to babies ($p < 0.05$).

Conclusions: Decreased paraoxonase activity in maternal serum may be considered as an additional risk factor for the development of low birth weight. It appears that PON1 activity plays an important role in infant development and affects birth weight. We think that the paraoxonase activity of the PON1 enzyme in mothers may be a marker in predicting the babies who are at risk in terms of birth weight.

Keywords: Birth weight, paraoxonase1 enzyme, lipid levels, maternal serum, baby cord blood

It is known that many factors affect the birth weight of the baby during pregnancy. Some of those are many anatomical, genetic, metabolic, endocrine causes such as nutritional disorders, low mother weight, chromosomal disorders, cigarette-alcohol consumption, gestational diabetes, hypertension, placental anomalies, drug use, cord anomalies, oligohydramnios. These causes negatively affect the development of the baby [1]. Various studies show that systemic and placental oxidative stress is also effective in this by making placental dysfunction [2]. Diseases associated with oxidative stress particularly affect newborns with low birth weight [3]. Low birth weight has been defined by the World Health Organization (WHO) as

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weight at birth of less than 2500 g (5.5 lb) [4]. Oxidative reactions occur with reactive oxygen radicals that will damage cells in the organism, and antioxidant mechanisms protect cells from this damage [5]. Many enzymes in the body have antioxidant effects. One of these is the Paraoxonase (PON) enzyme [6]. PON is a calcium-dependent ester hydrolase enzyme that is carried in the HDL structure in the blood and has high antioxidant effects. Mammals have three different PON genes (PON1, PON2 and PON3) on the same chromosome [7, 8]. PON1 is an enzyme with paraoxonase, arylesterase and lactonase activities that can react with a wide variety of substrates [9]. PON 1 can hydrolyze aryl and alkyl halides and organophosphates. It is synthesized in the liver and introduced into the bloodstream. PON1 protects both HDL and LDL from oxidation and can neutralize radicals [10]. Increased LDL oxidation in the serum creates endothelial damage and causes the formation of atheroma plaques. HDL dependent PON1 prevents this effect with its antioxidant feature. PON1 activity has been found to be low in people with potential risk for atherosclerosis such as diabetes, familial hypercholesterolemia, slow coronary flow [11, 12]. PON1 activity in newborns and premature babies is about half that in adults [13]. In a study, it was reported that maternal obesity increased susceptibility to oxidative damage in mother and newborn, and there was a decrease in PON-1 activity in both mother blood and cord blood [14]. Just as in the coronary arteries, studies are investigating the presence of plaque-disrupting plaques in placental vessels and their effect on fetal weight [15, 16].

This study aims to determine the relationship between lipid profile and PON1 enzyme activity in maternal venous blood and umbilical cord blood with birth weight, and to investigate whether this enzyme can be a marker for predicting babies at risk for birth weight.

METHODS

Patients/Volunteers and Ethics Statement

Eighty pregnant women who were hospitalized at Nenehatun Maternity Hospital (Erzurum-Turkey) and their newborn babies were included in our study. Twenty premature babies (among those born before 37th gestational week), 20 low birth weight babies (among those born at term but below 2500 grams), 20 normal-weight babies (among babies born at term), 20 postmature babies (among those born after 41st gestational week) was evaluated. Pregnant women between 18-40 years of age who had pregnancy follow-ups, without any chronic disease, no visual-hearing and communication disabilities, volunteering to participate in the study and signed the consent form were included in this study. In addition, cases with preeclampsia, gestational diabetes mellitus, intrauterine growth retardation and premature rupture of membranes were not included in the study. Babies with asphyxia, babies with respiratory distress syndrome, babies with severe anomaly and cardiac disease, babies with chorioamnionitis and infection in their mother, babies with the metabolic disease were excluded from the study.

The weight of mothers was measured just before birth, and venous blood samples were taken. Babies were divided into four groups: normal-weight babies (Group 1: Term), premature babies (Group 2: Pre-Term), low birth weight babies (Group 3: small for gestational age [SGA]), and postmature babies (Group 4: Post-Term). The weight of the newborns was measured and cord blood was taken. The samples were looked at HDL, LDL, total cholesterol, triglyceride levels and PON1 activities. Samples were taken into a straight biochemistry tube. The samples which will be measured PON1 activity was taken into the biochemistry tube, then centrifuged for 10 minutes at 4000 rpm,. After centrifuged, their serum was separated and kept in the freezer at -20 oC until the day of analysis.

This study was approved by the Clinical Researches of Ethical Committee of the Ataturk University (Erzurum-Turkey) (confirmation code: B.30.2.ATA.0.01.00/391).

Materials

Protein assay reagents, 4-nitrophenylacetate were purchased from Sigma–Aldrich Co. All other chemicals were analytical grade and obtained from Merck. Mother's venous blood samples and umbilical cord blood samples were taken from the Department of Obstetrics and Gynecology at a maternity hospital.

Serum Lipid Levels

In serum, lipid profile was evaluated with Cobas 6000-

501 module auto analyzer (Roche) by the photometric method.

PON1 Activity Assay

The whole PON1 activity procedure was performed according to our previous studies [10, 17]. Briefly, Paraoxonase activity of PON1 has been investigated with paraoxone (1 mM) in 50 mM glycine–NaOH (pH 10.5) buffer including 1 mM CaCl2 at 25°C. Enzyme activity assay is based on spectrophotometric measurement of p−nitrophenol at 412 nm. The molar extinction coefficient of paranitrophenol (ε = 18.290 M−1 cm−1 at pH 10.5) is used for the calculation of the activity. One enzyme unit was defined as the amount of enzyme that catalyzes the hydrolysis of 1 µmol of paraoxon at 25°C.

Protein Determination

To calculate the specific activity of the PON1 enzyme, protein assay was performed spectrophotometrically at 595 nm according to the Bradford method, using bovine serum albumin as the standard [10, 17].

Statistical Analysis

SPSS 23.0 software was used for statistical calculations. Descriptive statistics (mean, standard deviation, median, minimum and maximum values) were given for numerical variables while evaluating the data. In the study, the differences or relationships of other variables were examined according to the diagnostic variable. A cross table was created as a method for categorical variables and the Chi-Square test was applied. Kruskal-Wallis Test was used as a method for numerical variables. The purpose of the Kruskal-Wallis Test (sometimes also called the "one-way ANOVA on ranks") is to test the differences between three or more groups in groups that do not show normal distribution. When the data are examined, the diagnosis variable consists of four groups. The Kruskal-Wallis Test was used to examine whether there was a statistically significant difference between the groups in terms of variables. Statistical significance was taken as 0.05 in the analysis.

RESULTS

The analysis process of the research data has been examined under three headings. First, the distribution of variables and descriptive statistics are given. In the second stage, the relationship between gender, which is a categorical variable, and the diagnosis was given

Table 1. Descriptive statistics by groups

	Post-Term (n = 20)	Term (n = 20)	Pre-Term (n = 20)	SGA (n = 20)	*p* value
	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	
Age	25.10 ± 4.930	27.45 ± 5.763	26.05 ± 4.407	25.30 ± 5.713	0.373
Gravida	2.10 ± 1.553	2.55 ± 1.701	2.95 ± 2.012	2.05 ± 1.877	0.202
Parity	2.38 ± 1.188	2.33 ± 1.497	1.79 ± 1.188	2.00 ± 1.309	0.498

SGA = small for gestational age, SEM = standard error of mean

Table 2. Examination of the relationship between infant gender and diagnosis variable

			Post-Term	Term	Pre-Term	SAG	Total	Chi-Square	*p* value
Baby's Gender	Girl	Number	8	12	9	13	42	3.409	0.333
		Percent	19.0	28.6	21.4	31.0	100.0		
	Boy	Number	12	8	11	7	38		
		Percent	31.6	21.1	28.9	18.4	100.0		
Total		Number	20	20	20	20	80		
		Percent	**25.0**	**25.0**	**25.0**	**25.0**	**100.0**		

by cross-tables method and chi-square test. In the third stage, the Kruskal-Wallis Test was used to examine whether there was a significant difference between numerical variables according to diagnoses.

Descriptive Statistics

Participants (n = 80) are presented in Table 1 with their mean values and standard deviations.

Cross Table Method and Chi-Square Analysis

Table 2 shows whether there is a dependent relationship between gender and the diagnosis variable. At the same time, the frequent values and percentage values in the diagnosis variable of the sexes were also shown.

When the chi-square test is examined, we can say that there is no statistically significant relationship between gender and diagnosis ($p > 0.05$).

Table 3 prensents whether there is a difference between the diagnosis variable and t variables. Kruskal-Wallis Test result values and p values were also given along with the median, minimum and maximum values of the variables. The p-values have been evaluated to decide whether there is a statistically significant difference.

According to our results, there was no statistically significant difference between maternal values except PON1 paraoxonase activity levels ($p > 0.05$). These values are maternal's age, gravida, parite, TG, Total cholesterol, HDL and LDL. There was a statistically significant difference in all values belonging to babies ($p < 0.05$). These values are the baby's weight, TG, Total cholesterol, HDL, LDL and PON1.

The maternal PON1 level of the Pre-Term was significantly lower than the Term, Post-Term, and SGA groups. In addition, maternal PON 1 level of Term group is significantly higher than SGA group.

The baby weight of the Pre-Term and SGA groups was significantly less than the Term and Post-Term groups.

The Total cholesterol level of the Pre-Term group was significantly higher than the Post-Term and SGA groups. The TG level of the SGA group was significantly higher than the Term and Pre-Term groups. The HDL level of the Pre-Term group was significantly higher than the Post-Term and SGA groups. The LDL level of the Pre-Term group was significantly higher than the Post-Term and SGA groups.

The baby PON1 level of the Pre-Term and SGA groups was significantly lower than the Term and Post-Term groups.

DISCUSSION

The weight of the newborn is affected by many factors such as the mother's nutrition, socio-economic status, diseases, environmental conditions and genetics. It is directly related to the adaptation of the baby to the external environment. For this reason, it is very important that the baby is born at the optimum weight [1]. Various studies are showing the relationship between maternal weight and lipid profile with newborn weight. In the study of Ouidir *et al*. [18], it was reported that maternal lipids affect fetal development. In a study by Brittos *et al*. [19], it was reported that there was a relationship between maternal weight, newborn weight and lipids in the umbilical cord blood. Kim *et al*. [20] conducted a study on the effect of oxidative stress on birth weight in pregnant women. They reported that the levels of malondialdehyde, one of the main products of lipid peroxidation and an indicator of the oxidant-antioxidant balance of the placenta, in maternal urine were high, and the birth weight of the babies of these mothers was low. It has been reported that maternal oxidative stress may affect birth weight in this study [20]. Negi *et al*. [21] conducted a study on the evaluation of biomarkers of oxidative stress and antioxidant capacity in cord blood of preterm newborns with low birth weight. In this study, it was reported that oxidative stress was high especially in babies born with low birth weight, and morbidity and mortality increased in these babies. Oxidative stress is also higher in newborn babies, as antioxidant defense mechanisms are not fully mature and oxidant loads are high [21]. In another study by Negi *et al*. [3], they found a significant increase in malondialdehyde and 8-Hydroxy-2-deoxy guanosine (one of the markers of oxidative DNA damage) levels in premature babies with low birth weight. It has been reported that the weight of the newborn baby is important in terms of oxidative stress, morbidity and mortality [3]. In our study, we determined the PON1 enzyme activity as an antioxidant. This enzyme is half the size of the newborn in the adult human and rises to the adult level one year after birth and remains con-

Table 3. Examination of the difference between variables based on diagnoses

		Median	Minimum	Maximum	K.W.	*p* value
Maternal TG	1) POST-TERM	250.00	60.00	376.00	6.185	0.103
	2) TERM	194.50	118.00	406.00		
	3) PRE-TERM	223.00	122.00	268.00		
	4) SGA	276.50	102.00	357.00		
Maternal Total Cholesterol	1) POST-TERM	276.00	51.00	398.00	4.719	0.194
	2) TERM	277.00	187.00	398.00		
	3) PRE-TERM	253.50	147.00	525.00		
	4) SGA	218.00	178.00	381.00		
Maternal HDL	1) POST-TERM	68.00	23.00	98.00	6.915	0.075
	2) TERM	80.50	40.00	105.00		
	3) PRE-TERM	74.00	38.00	125.00		
	4) SGA	64.00	44.00	106.00		
Maternal LDL	1) POST-TERM	134.50	16.00	272.00	3.739	0.291
	2) TERM	147.50	86.00	370.00		
	3) PRE-TERM	147.50	66.00	300.00		
	4) SGA	117.00	61.00	266.00		
Maternal PON1	1) POST-TERM[b]	130.70	119.30	151.00	59.004	**< 0.001***
	2) TERM[b]	138.50	126.30	146.30		
	3) PRE-TERM	103.60	95.20	107.80		
	4) SGA[a, b]	111.20	92.90	177.00		
Baby Weight	1) POST-TERM[b, c]	3282.50	2700.00	3850.00	57.174	**< 0.001***
	2) TERM[b, c]	2980.00	2605.00	3900.00		
	3) PRE-TERM	2440.00	1800.00	2860.00		
	4) SGA	2400.00	2200.00	2470.00		
Baby Total Cholesterol	1) POST-TERM[b]	52.00	37.00	80.00	15.776	**0.001***
	2) TERM	63.00	38.00	268.00		
	3) PRE-TERM	67.00	57.00	217.00		
	4) SGA[b]	57.50	34.00	70.00		
Baby TG	1) POST-TERM	32.50	23.00	88.00	14.788	**0.002***
	2) TERM [c]	32.00	17.00	242.00		
	3) PRE-TERM[c]	30.00	16.00	60.00		
	4) SGA	50.50	22.00	82.00		
Baby HDL	1) POST-TERM[b]	26.50	18.00	46.00	18.385	**< 0.001***
	2) TERM	28.00	18.00	108.00		
	3) PRE-TERM	33.50	25.00	45.00		
	4) SGA[b]	24.00	13.00	39.00		
Baby LDL	1) POST-TERM[b]	20.50	6.00	37.00	25.997	**< 0.001***
	2) TERM	25.50	7.00	112.00		
	3) PRE-TERM	30.00	16.00	68.00		
	4) SGA[b]	19.00	8.00	32.00		
Baby PON1	1) POST-TERM[b, c]	52.60	43.80	55.70	58.310	**< 0.001***
	2) TERM[b, c]	51.85	45.20	57.30		
	3) PRE-TERM	37.80	31.80	44.70		
	4) SGA	43.80	40.70	51.20		

K.W. = Kruskal Wallis Analysis *$p < 0.05$ (Statistically significant). Significance against TERM group, [a]$p < 0.05$; significance against PRE-TERM group, [b]$p < 0.05$; significance against SGA group, [c]$p < 0.05$.

stant throughout life. It does not differ according to gender [13]. Therefore, we did not discriminate regarding the gender of the babies in our study. It has been reported that PON1 activity decreases in cases of increased oxidative stress such as dyslipidemia, diabetes mellitus, hypertension, advanced maternal age, and cigarette-alcohol consumption [22]. Ferretti *et al*. [14] evaluated leptin and PON1 activity in the cord blood of obese mothers. In this study, it was concluded that PON1 activity decreased in obese women compared to normal weight, and oxidative damage increased in mother and baby [14]. Mogarekar *et al*. [23] investigated the relationship between newborn birth weight and maternal serum PON1 arylesterase activity and found a positive correlation between them. And in their study, it was stated that this situation may be an additional risk factor in low birth weight babies [23].

Some researchers have explored the relationship between PON1 activity and pregnancy complications [24, 25]. Kumru *et al*. [25] have shown in their study that PON1 activity decreased in preeclamptic pregnancies. Lawlor *et al*. [24] indicated in their study that there is a close relationship between PON-1 Q192R polymorphism and preterm birth. Our study also supports these studies. We revealed that the paraoxonase activity of the PON1 enzyme in mothers affects both the gestational week and may be a marker in predicting the babies who are at risk in terms of birth weight.

CONCLUSION

To conclude, we can say that mothers with low paraoxonase activity of PON1 enzyme are more likely to deliver a baby with low birth weight. It appears that PON1 activity plays an important role in infant development and affects the birth weight of a newborn. Decreased paraoxonase activity in maternal serum may be considered as the additional risk factor for the development of low birth weight newborns. We think that the paraoxonase activity of the PON1 enzyme in mothers may be a marker in predicting the babies who are at risk in terms of birth weight.

Authors' Contribution

Study Conception: ED, BK; Study Design: ED, BK, AN; Supervision: ED, BK; Funding: ED, BK, AN; Materials: BK, AN; Data Collection and/or Processing: ED, BK, AN; Statistical Analysis and/or Data Interpretation: ED, BK; Literature Review: ED, BK, AN; Manuscript Preparation: ED, BK and Critical Review: ED.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of the correlation between perfusion index and prognosis in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objectives: This study aims to investigate whether perfusion index (PI) values, which are measured non-invasively, affect emergency management, especially in hospitalization and discharge decision in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods: Patients who were admitted to the emergency department of Okmeydanı Training and Research Hospital with a COPD exacerbation in 3-months period and who volunteered to participate were included in the study. Vital parameters and PI values of the patients at the time of admission, at the first, second and third hour of the admittance and at the time of hospitalization (in the case of hospitalization) were recorded. The patients were treated for COPD exacerbation according to the Global Initiative for Chronic Obstructive Lung Disease 2011 guide and the decision of discharge, hospitalization in the emergency department, andhospitalization in the intensive care unit was taken based on the relevant guideline.

Results: A total of 57 patients were included in the study. Of the patients, 45 (78.9%) were male. The mean age of the patients was 65.65 ± 9.90 years. There was no statistically significant difference in arrival vital parameters and PI in terms of the gender ($p > 0.05$). The change between PI values at the time of admission and the first hour in the patients admitted to intensive care unit was found to be significantly lower compared to patients who were hospitalized in the emergency department or discharged ($p = 0.035$; $p = 0.033$). The difference between the PI values at the time of admission and at the third hour of the follow up of the discharged patients was found to be significantly higher compared to the hospitalized patients ($p = 0.035$). There was no statistically significant difference between the arrival PI measurements in terms of the presence of comorbid diseases ($p > 0.05$).

Conclusions: Considering the hourly changes, the PI values of patients admitted to the emergency department with COPD exacerbation may be helpful in predicting the decision of discharge, hospitalization in the emergency department or intensive care unit.

Keywords: Emergency department, chronic obstructive pulmonary disease, perfusion index

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Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, treatable, chronic and progressive lung disease developing as due to the chronic inflammatory process against harmful gases and particles, particularly cigarette smoke. Inflammation is not only restricted to the lungs, but has systemic features. COPD exacerbation and comorbidities may affect the natural course of the disease [1, 2].

COPD is one of the most important causes of morbidity and mortality worldwide. The World Health Organization (WHO) predicts that COPD, the fourth cause of mortality in the world in 2004, will have been the third by 2030. Within this scope, more than 90% of morbidity and mortality in low and middle income countries are thought to be related to COPD [3, 4].
Adequate tissue perfusion is vital in maintaining metabolic processes in cells, repairing tissue and developing resistance to infectious organisms [5]. Many clinical studies have demonstrated that early correction of tissue hypoxia in critical patients and providing systemic oxygen support may decrease the incidence of mortality and morbidity [6].

The perfusion index is an indirect and noninvasive measurement of peripheral perfusion. It is calculated with the pulse oximeter by measuring the percentage of the pulsatile signal to the non-pulsatile signal, and both values are obtained from the absorbed infrared light. Perfusion index value may vary depending on the measured area (finger, toe). In the monitoring of peripheral perfusion, Doppler flowmeter, capillary microscopy, transcutaneous oximeter, and sublingual capnometry can be used. However, PI measurement is important in terms of bedside evaluation, easy application, early detection of organ dysfunction, and early intervention [7].

Time is of the essencein the initial resuscitation and treatment of emergency patients. Therefore, the use of non-invasive parameters is recommended as an alternative approach to other methods to identify hemodynamically unstable patients. Non-invasive imaging systems are more appropriate for early identification of hemodynamic status in emergency patients [8].

This study aims to investigate whether non-invasively measured perfusion index (PI) values in COPD patients affect the emergency management, especially on the hospitalization and discharge decision.

METHODS

The study was designed as a single-center, prospective, cross-sectional, and descriptive study.Prior to the study, ethical approval was obtained from the Turkish Medicines and Medical Devices Agency, Okmeydanı Training and Research Hospital (TRH), Planning Board of Education. The study was conducted with the approval of OkmeydanıTRH Clinical Research Ethics Committee dated 18.11.2014 and numbered 242. The study population consisted of patients admitted to the emergency department of Okmeydanı TRH with COPD exacerbation in 3-months period. For the calculation of sample size we used formula (n=Nt2pq/d2(N-1)+t2pq) and minimum of 50 total amount of cases found.

Patients over 18 years of age with a diagnosis of COPD and admitted to our emergency medicine clinic due to COPD attack and patients who agreed to participate in the study and informed consent form signed by the patients himself or his first degree relative at the time of application to the emergency department were included to the study.

Exclusion criteria of the study were when patients under the age of 18 years old, patients who did not agree to participate in the study and patients who didn't diagnosed with COPD. No patient met these exclusion criteria of the study.

The patients were treated for COPD exacerbation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 guide and the decision of discharge, hospitalization in the emergency department, and hospitalization in the intensive care unit was taken based on the relevant guideline.In patients who were followed up with COPD exacerbation, PI values at the time of admission, at the first, second, and third hour of the admittance, and at the time of hospitalization in the case of hospitalization were measured by a different physician with the Masimo Pulse Co-oximeter Rad-57 from the second, third or fourth finger for at least 10 seconds. Vital parameters at the time of arrival (body temperature, pulse, blood pressure, O_2 saturation) as well as age, gender, the presence of comorbid disease and used drugs written on the triage cardwere recorded in the case report form. Therefore, the treatment process and the decision taken about the patient (hospitalization, need for intensive care, discharge) according to the guideline

suggestions were recorded in the aforementioned form.

Patients over the age of 18 who were diagnosed with COPD and admitted to emergency department due to COPD exacerbation, and whose voluntary consent form could be signed by the patient or a first degree relative at the time of emergency admittance were included in the study. Patients under 18 and who did not agree to participate were excluded.

Statistical Analysis

In the statistical analysis, Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 Statistical Softwares (Utah, USA) were used. In addition to descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Rate, Minimum, and Maximum), Mann Whitney U test was used to compare groups having non-normally distributed parameters. Kruskal Wallis Test was used for comparisons of three or more groups not showing normal distribution, and Mann Whitney U test was used to determine the group causing the difference. Wilcoxon signed-rank test was used for intra-group comparisons of groups having non-normally distributed parameters. Fisher-Freeman-Halton test was used to analyze qualitative data. Pearson and Spearman correlation analysis was used to examine the relationships between parameters. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 57 participants were included in the study. The mean age was 65.65 ± 9.90 years, the mean pulse rate was 102.37 ± 16.34, and the mean body temperature was 36.92 ± 0.69 °C. The most common comorbidities were hypertension with 35.6% (n = 21) and ischemic heart disease with 33.9% (n = 20) (Table 1).

The length of stay in the emergency service ranged from 1 to 5 hours, with a mean of 2.79 ± 0.77 hours. No hospitalization was observed in 75.4% (n = 43) of the cases, while 14.1% (n = 8) were hospitalized in the emergency service and 10.5% (n = 6) were admitted to the intensive care unit.

The arrival PI measurements of the cases ranged from 0.13 to 17, with a mean of 4.56 ± 3.58 (Table 2).

According to the results, pulse, systolic, diastolic and body temperature measurements did not show sta-

Table 1. Distribution of descriptive parameters

Age (years), Mean ± SD	65.65 ± 9.90
Gender, n (%)	
Female	12 (21.1)
Male	45 (78.9)
Blood pressure (mmHg), Mean ± SD	
Systolic	147.84 ± 33.89
Diastolic	80.67 ± 17.80
Pulse, Mean ± SD	102.37 ± 16.34
Body temperature (C^0), Mean ± SD	36.92 ± 0.69
Saturation (%), Mean ± SD	88.74 ± 9.16
Comorbidities*, n (%)	
Lung cancer	1 (1.7)
Diabetes	6 (10.2)
Hypertension	21 (35.6)
Ischemic Heart Disease	20 (33.9)
Congestive Heart Failure	9 (15.3)
Chronic renal failure	2 (3.4)

*Multiple options are marked

Table 2. Distribution of the length of stay, hospitalization status and PI measurements

	n	Mean ± SD
Arrival PI	57	4.56 ± 3.58
1st hour PI	57	5.65 ± 3.48
2nd hour PI	56	5.81 ± 2.90
3rd hour PI	36	6.00 ± 3.07
Hospitalization PI	14	5.57 ± 3.62

tistically significant difference in terms of the age distribution of the cases ($p > 0.05$).

The percentage of saturation of patients without hospitalization was found to be significantly higher than those who were hospitalized in the emergency department and the intensive care unit ($p = 0.001$).

There was no statistically significant difference between the distribution of the hospitalization results of the patients according to gender ($p > 0.05$) (Table 3).

According to the arrival PI measurement, the mean increase of 1.09in PI measurement at the first hour was found statistically significant ($p = 0.001$). According to the arrival PI measurement, the mean increase of 0.68 in PI measurement at hospitalization was not statistically significant ($p > 0.05$) (Table 4).

The results showed a statistically significant difference between the arrival PI measurements of the cases ($p = 0.043$). According to the results of Mann Whitney U Test conducted to determine the difference, it was found that the arrival PI values of the patients who were hospitalized in intensive care unit were significantly higher than the patients hospitalized in the emergency department ($p = 0.039$). There was no significant difference between other groups ($p > 0.05$).

According to the arrival PI measurement of the patients, it was concluded that there was a statistically

Table 3. Evaluation according to the decision

		Decision			*p* value
		No Hospitalization (n = 43)	**Emergency Service Hospitalization (n = 8)**	**Intensive Care Hospitalization (n = 6)**	
Age	**Min-Max (Median)**	50-83 (66)	58-80 (65.5)	51-82 (68.5)	**0.963[c]**
Pulse	**Min-Max (Median)**	70-140 (100)	70-130 (107.5)	90-130 (115)	**0.193[c]**
SBP	**Min-Max (Median)**	90-220 (143)	106-220 (129.5)	76-2010 (137)	**0.931[c]**
DBP	**Min-Max (Median)**	50-119 (80)	50-122 (82.5)	45,120 (75.5)	**0.764[c]**
Body temperature	**Mean ± SD**	36.89 ± 0.65	37.23 ± 0.95	36.68 ± 0.55	**0.438[c]**
Saturation (%)	**Min-Max (Median)**	78-98 (94)	55-96 (85)	65-87 (77)	**0.001[c]****
		n (%)	**n (%)**	**n (%)**	
Gender					
	Female	8 (66.7)	2 (16.7)	2 (16.7)	**0.648[d]**
	Male	35 (77.8)	6 (13.3)	4 (8.9)	
Comorbidities					
	No	14 (70.0)	3 (15.0)	3 (15.0)	**0.737[d]**
	Yes	29 (78.4)	5 (13.5)	3 (8.1)	

[c]Kruskal Wallis Test, [d]Fisher Freeman Halton Test, **$p < 0.01$, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure

significant difference between the changes at the first hour PI measurement ($p = 0.049$). According to the arrival PI measurement of patients in intensive care unit, the change in PI measurement at the first hour was found to be significantly lower than those without hospitalization and who were hospitalized in the emergency department ($p = 0.035$). There was no significant difference between other groups ($p > 0.05$).

The results demonstrated no statistically significant difference between the changes in the second hour PI measurement according to the arrival PI measurement ($p > 0.05$). However, it was seen that there was a statistically significant difference between the changes in the third hour PI measurement according to the arrival PI measurement ($p = 0.045$). In terms of the arrival PI measurement, the change in the third hour PI measurement of the non-hospitalized patients was found to be significantly higher than the patients who were hospitalized in the emergency department ($p = 0.035$). There was no significant difference between other groups ($p > 0.05$) (Table 5).

The positive correlation between arrival PI measurements and hospitalization PI measurements of the patients participating in the study (increasing hospitalization PI values with increasing arrival PI values)at %73.5 level was found to be statistically significant ($r = 0.735$; $p = 0.003$) (Fig. 1).

DISCUSSION

This study aims to investigate the correlation between PI values and hospitalization and discharge decision in COPD patients and to determine whether

Table 4. Evaluation of the difference between arrival PI and the first, second, and third hour PI measurements

	Perfusion Index (PI)		p[e] value
	Mean ± SD	Difference	
Arrival PI (n = 57)	4.56 ± 3.58	-1.09 ± 1.98	**0.001****
1st hourPI (n = 57)	5.65 ± 3.48		
Arrival PI (n = 56)	4.34 ± 3.19	-1.47 ± 2.18	**0.001****
2nd hourPI (n = 56)	5.81 ± 2.90		
Arrival PI (n = 36)	4.09 ± 3.57	-1.91 ± 2.49	**0.001****
3rdhourPI (n = 36)	6.00 ± 3.07		
Arrival PI (n = 14)	4.88 ± 4.46	-0.68 ± 2.35	**0.327**
Hospitalization PI (n = 14)	5.57 ± 3.62		

[e]Wilcoxon Signed Ranks Test, **$p < 0.01$

Table 5. Evaluation according to the decision

		Decision			p value
		No Hospitalization (n = 43)	Emergency Service Hospitalization (n = 8)	Intensive Care Hospitalization (n = 6)	
Arrival PI	**Mean ± SD**	4.46 ± 3.30	2.85 ± 2.73	7.60 ± 5.08	**0.043[c]***
Arrival-1st hour PI	**Mean ± SD**	-1.33 ± 1.85	-1.45 ± 1.52	1.10 ± 2.37	**0.049[c]***
Arrival-2nd hour PI	**Mean ± SD**	-1.72 ± 2.20	-1.36 ± 1.25	0.18 ± 2.54	**0.298[c]**
Arrival-3rd hour PI	**Mean ± SD**	-2.72 ± 2.23	-0.69 ± 1.64	-0.23 ± 3.11	**0.045[c]***

[c]Kruskal Wallis Test, *$p < 0.05$, **$p < 0.01$

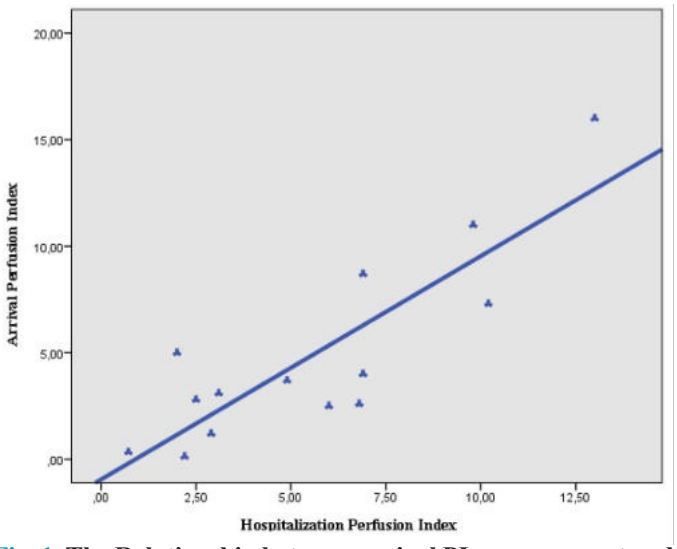

Fig. 1. The Relationship between arrival PI measurement and hospitalization PI measurement.

patients' follow-ups can be performed noninvasively.

The prevalence of COPD also increases with age. In a study conducted by Hong *et al*. [9], the mean age of the patients with COPD in China was found to be 67.7. Nunez *et al*. [10] found the mean age of COPD patients living in Europe as 66.6. In a study conducted in our country, the mean age of patients with COPD was found to be 63.5 [11]. In our study, the mean age was 65.6, which is consistent with the literature.

Most studies have shown that the prevalence of COPD in males is higher than that of females [9, 10]. However, the data obtained in developed countries have revealed that the prevalence is almost equal between females and males, which is thought to reflect changes in the smoking habits [12]. In our study, it was seen that the number of males were considerably higher than that of females. It is thought that this difference is due to the fact that smoking is more common among males in our country.

It can be seen in the literature that approximately two out of every three COPD patients have one or more comorbidities. These include cardiovascular diseases (CVD), lung cancer, and thromboembolic diseases [13]. In the study investigating comorbidity prevalence in COPD patients, it was found that CVD was 2 times and hypertension was 1.6 times higher than normal population, and more hospitalization was observed in those patients. In addition, it was observed that the frequency of diabetes increased with COPD, even in the mild stage [14]. In a study investigating heart failure in patients with COPD, the frequency of heart failure associated with coronary atherosclerosis was found to be 20% [15]. Although COPD is an independent risk factor for lung cancer, it increases lung cancer risk 2-5 times compared to smokers without COPD [16]. In a cross-sectional study conducted on 514 patients with COPD in 25 centers in Turkey, at least more than half of the COPD patients were shown to have comorbidities. The most common comorbid diseases were cardiovascular diseases with 30.4%, sleep disorders with 20.2%, and hyperlipidemia with 15.8% [17]. In our study, one or more comorbid diseases were found in 65% of the cases.

In hospitals, different diagnostic models have been used for the last thirty years to predict the mortality of patients, particularly in adult intensive care patients [18]. Although many invasive and non-invasive methods have been used, there are no studies in the literature revealing the relationship between perfusion index with hospitalization and discharge of patients with COPD exacerbation.

The mean arrival perfusion index of the patients in this study was found to be 4.56.In a study investigating the non-invasive examination of peripheral perfusion in intensive care patients, Lima *et al*. [19] compared 108 healthy adult and 37 intensive care patients and found the critical PI value as 1.4. They concluded that the values below this value suggest the presence of poor peripheral perfusion [19]. However, the device used in that study was different from the Masimo Pulse Co-Oximeter Rad-57 (The device used in our study), the range of values to be measured were between 0.3 and 10.0. In that study, a threshold value for PI could not be determined due to the absence of a statistically significant difference between the hospitalized and discharged patients. This may be due to the fact that the cases were only COPD exacerbation cases and the number of the cases was relatively low. In a study comparing invasive and non-invasive methods to demonstrate peripheral circulatory disorders in intensive care patients, changes in peripheral perfusion for poor prognosis were found to be a better indicator than fingertip oxygen saturation [20]. In another study investigating whether PI values would be used as a prognostic indicator in intensive care patients, it was concluded that patients with low PI values had organ failure faster [7]. Unlike the other studies, there was no statistically significant difference between admission PI values of the discharged patients and patients

hospitalized in the emergency department or intensive care unit, who can be considered as critical patients. In a study investigating the relationship between PI values and mortality in intensive care patients in 2013, it was concluded that perfusion index values were effective in predicting mortality [21]. During this study, no mortality was seen inthe patients with COPD exacerbation who were admitted to the emergency department. Long-term patient follow-up was not performed in the study. Therefore, its relationship with mortality could not be determined.

In addition to the studies favoring the perfusion index to predict the perfusion status and mortality of the patients, there are also studies claiming the opposite. In a study, the effect of perfusion worsening due to the sepsis on pulse oximetry was questioned and whether the perfusion index is a marker of poor peripheral perfusion was investigated. It was reported in that study that the perfusion index of anesthetized rabbits was not useful in terms of increased risk [22]. Similarly, in our study, the arrival PI values of the patients admitted to intensive care unit were found to be significantly higher than the arrival PI values of the patients who were hospitalized in the emergency department or discharged.

Limitations

This study may have some limitations. First of all, the most important limitationsof this studyare that the study is single-centered and the number of patients is low.Because of some of the blood gases taken from the patients were venous and the others were arterial blood gases, standardization could not be done, so they were not included in the study. The normal value range or a cut-off value fort he PI was not calculated.

CONCLUSION

With the first hour PI changes, it is possible to predict that the patient's response to the treatment may be poor and the patient may be taken to the intensive care unit. Considering the third hour PI of the patients, it may be possible to predict the decision of discharge or hospitalization. In conclusion, there is no significant relationship between the arrival PI values and the discharge or hospitalization of the patients admitted to the emergency department with COPD exacerbation. The number of studies investigating the relationship between PI and prognosis is low in the literature and it is thought that it will be appropriate to conduct studies in larger series.

Authors' Contribution

Study Conception: MD, BC; Study Design: MD, BC, BMA; Supervision: MD, BC, BMA; Funding: MD, BC, BMA; Materials: MD, BC, BMA; Data Collection and/or Processing: MD, BC; Statistical Analysis and/or Data Interpretation: MD, BC, BMA; Literature Review: MD, BC, BMA; Manuscript Preparation: MD, BC, BMA and Critical Review: MD, BC, BMA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(1):24-30 Original Article

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The quality of life of the elderly is negatively affected by pertrochanteric femoral fractures: a comparative study

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ABSTRACT

Objectives: Limited data is available regarding the quality of life of hip fracture patients following surgery. This study examined the mid-term quality of life of hip fracture patients and compared these patients with healthy elderly patients devoid of hip fractures.

Methods: A total of 103 patients (aged > 65 years) with pertrochanteric femoral fractures were treated with proximal femoral nail surgery in our clinic between January 2012 and December 2016. A healthy control group (n = 100) was demographically matched to the patients. The final follow-up visit included their Harris Hip Score and completion of a Short Form-36. The eight sub-parameters from the Short Form-36 form were also assessed.

Results: The mean follow-up time for the patients was 36.4 ± 12.3 (range, 24-72) months. The mean Charlson comorbidity score for the patient group was 4.4 ± 2.1 and the mean Harris Hip Score was 77.24 ± 10.2. The comparison of the Short Form-36 sub-parameters revealed that the quality of life of the patient group was found to be lower than that of the control group for the following parameters physical function, physical roles, vitality, and social function ($p < 0.05$).

Conclusions: Even if the fracture had healed of patients with hip fractures, QoL related to physical and social functions was not improved accordingly, new healthcare policies should be developed for these patients based on the premise that their physical capacity may not be fully regained. Moreover, the importance of hip fracture prevention was demonstrated by this study.

Keywords: Hip fracture, aged, quality of life, Short Form 36, morbidity

Hip fractures generally occur in patients aged > 65 due to a low-energy trauma. These fractures constituted significant proportion traumas in elderly (aged > 65 years) and account for 38% of all extremity fractures [1]. Approximately 2.3 million hip fractures per year are expected by 2050 owing to increased aging population [2]. Non-surgical treatment of hip fractures has high mortality rates [3]. Thus, surgical treatment is recommended as earlier as possible to mobilize the patients at the earliest convenience. It has been reported that patients who were operated due to a hip fracture in the first 48 hours and mobilized in the early period have significantly lower mortality rates [4, 5]. In pertrochanteric fractures, osteosynthesis is the aim of the surgical treatment because of its metaphyseal location. Previous studies in the literature have

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shown high union rates and high hip scores with osteosynthesis of pertrochanteric fractures [6, 7].

Some patient dependent factors could negatively affect the healing following surgical treatment of hip fractures, such as the development of nutritional problems, dementia, or Alzheimer's disease, reduced mobilization capacity and prolonged hospitalization [8, 9]. Furthermore, elderly hip fracture patients have diminished ability to continue living independently which directly related to their hip scores. It remains unclear whether these patients can achieve a quality of life (QoL) equivalent to that of their peers despite a successful osteosynthesis of the hip fracture. Effective treatment for hip fracture patients should include physical, mental, and social improvement. Since some studies have reported a decrease in the physical, mental, and social aspects of their patients following hip fractures which lead to a decrease in patients' well-being. Thus, the reversibility of this decreased QoL deserves evaluation. However, the literature regarding this subject has conflicting results. Some studies have included a limited number of patients and short-term results, whereas other studies have provided few information regarding physical deterioration, mental, or social deterioration [10, 11]. While a few studies of the musculoskeletal system diseases in Turkey have evaluated QoL issues, to the best of our knowledge, there has been no previous study that has evaluated the QoL for a morbid pathology such as a hip fracture.

This study examined the mid-term healing and improvement of the QoL in elderly patients following hip fractures and compared with a healthy matched population.

METHODS

Patients and Study Design

The patient records were examined for 167 elderly patients that were surgically treated for pertrochanteric femoral fracture in our clinic between January 2012 and December 2016. The design and protocol of this retrospective study were approved by the hospital Institutional Review Board (permit no: 4328876-929/20.02.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki. This study included 103 patients who were aged > 65 years and surgically treated with a proximal femoral nail (PFN). The patients excluded who could not be contacted during follow-up (n = 5), who were treated with a hemiarthroplasty (n = 5), who were treated with dynamic hip screw (DHS) (n = 2), who were exitus during follow-up (n = 43), did not meet reduction criteria and had lag screw malpositioning (n = 5), nonunion and revision surgery (n = 8; 4 cut-out, 2 varus collapse, and 2 non-mechanical cause). A written informed consent was obtained from each patient. The demographic data and Charlson comorbidity scores of the patients were then recorded. The fractures were classified according to the AO classification system. The mean follow-up period was 36 months (range, 24-72 months). The overall mortality rate was determined to be 26%. In 4 (4%) patients had cut-out.

A control group (n = 100) was formed of randomly selected from patients aged > 65 years who were living in the same geographic area without a hip pathology and matched to the patients via their demographic data. The patients were evaluated with the Harris Hip Score (HHS) and interviewed with the Short Form-36 (SF-36). The SF-36 form evaluates 8 sub-parameters, which includes physical function, physical role, bodily pain, general health, vitality, mental health, emotional role, and social function (Fig. 1). Then the physical, mental, and social QoL was evaluated by comparing the sub-parameters for the patients and the control group.

Clinical Treatment and Surgical Techniques

Mechanical and medical DVT prophylaxis was started immediately following admission to the hospital. Following the completion of the necessary preparations for anesthesia, surgery was performed as early as the general medical status of the patient allowed. Surgery was performed at a mean of 3.9 days (range, 1-9 days) following admission.

Infection prophylaxis was administered to all patients with i.v. cefazolin preoperatively. During the surgical procedure, initially closed reduction was tried under traction in the supine position. Closed reduction was often successful but 10 (10%) patients required direct reduction maneuvers. The reduction quality was confirmed with fluoroscopy in the anteroposterior (AP) and lateral planes. The proximal femoral nail was implanted as previously described techniques [12]. The operation was ended following the final fluoroscopic confirmation of the fracture and the nail.

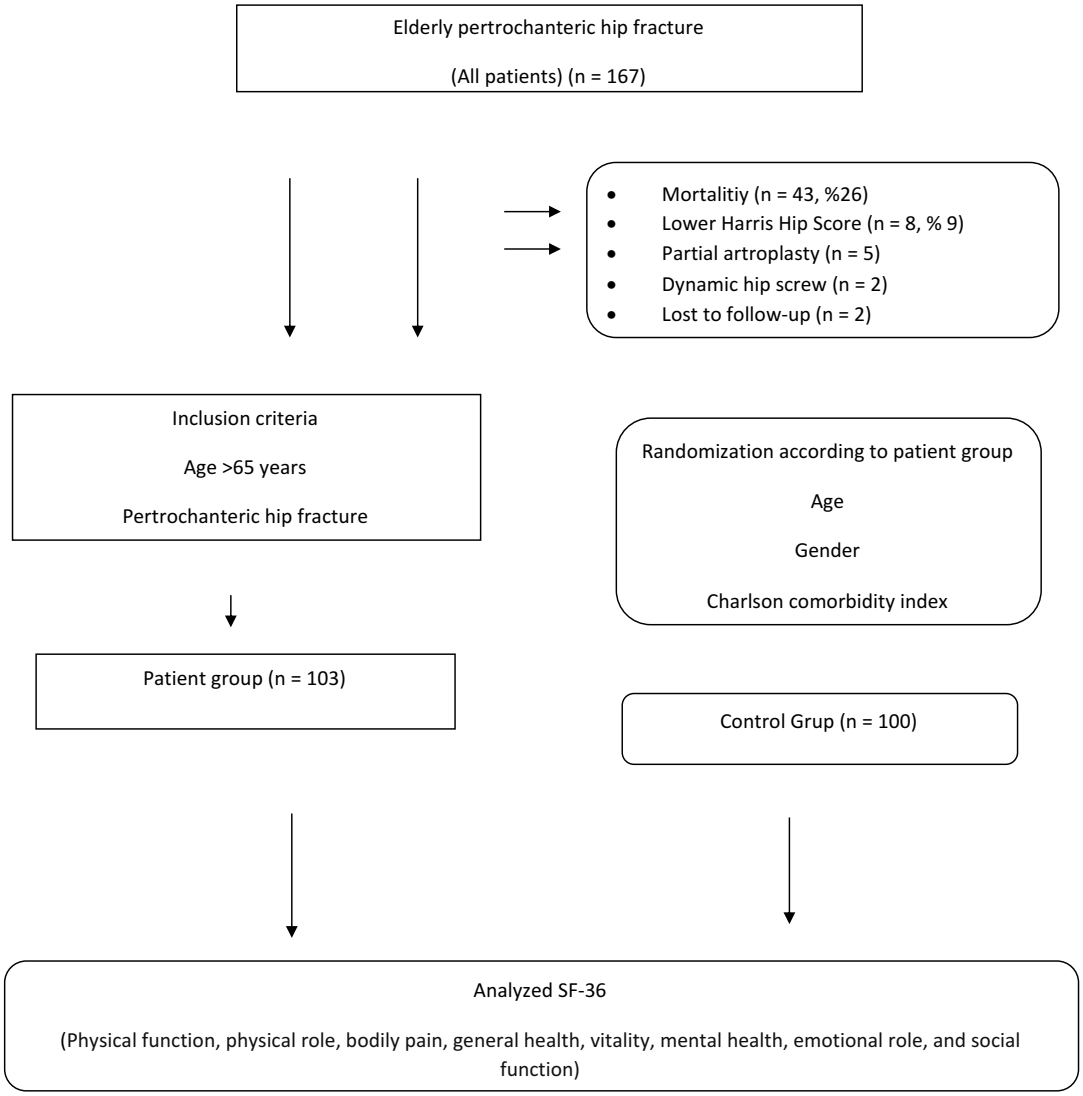

Fig. 1. Patients and study design

In the current study, two nailing systems, PFNA (Synthes GmbH, Oberdorf, Switzerland) or PTN (Biomet, Warsaw, Indiana, USA), were used. Varus malreduction of < 120 mm or displacement of > 10 mm was not accepted. The lag screw was placed at < 20 mm Baumgartner's tip-apex distance [13, 14]. One distal static interlocking screw was used in all patients.

Follow-up

The patients were mobilized with a walker on the postoperative first or second days. Weight-bearing was permitted as tolerated in all patients. Timing of full weight-bearing was decided based on fracture classification: at 6th week for A1 and A2 fractures, at 12th week for A3 fractures, respectively. The patients were followed-up with 2-week intervals until bone union occured and range of motion angles were noted. Patients with union continued to be followed up with annual controls. Bone nonunion and implant failure were checked radiologically. In the follow-up examinations, union and cut-out, cut-true, varus collapse, and lateral sliding were checked. At the final follow-up examinations, the patients were evaluated with the HHS and SF-36 [15, 16]. The HHS system and a questionnaire SF-36 form. The HHS system incorporates a points system with 90-100 points indicating an excellent result, 80-89 points is good, 70-79 points are fair, and < 70 points indicates a poor result.

Statistical Analysis

Data obtained in this study were analyzed statistically using SPSS v.22 software, and at a confidence

interval of 95%. Qualitative data were stated as the frequency distribution, and quantitative data were stated as the mean, minimum, and maximum values. Demographic data were evaluated with the Mann Whitney U-test. The HHS and the 8 sub-parameters of the SF 36 of the patients and control group were evaluated with the Mann Whitney U-test. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The mean age of the subjects was 75.2 ± 12 years (range, 65–93 years) in the patient group and 73.4 ± 10.4 years (range, 65–90 years) in the control group. The gender ratio (F/M) was 2/1 for both the patient and control groups. The mean Charlson comorbidity score was 4.4 ± 2.1 (range, 1-7) in the patient group and 4.1 ± 1.9 (range, 1-6) in the control group. According to the AO classification, 44% of the fractures were AO 31A1, 34% were AO 31A 2, and 23% were AO 31A 3. No statistically significant differences were found between the patient and control groups with respect to their demographic data ($p > 0.05$) (Table 1).

The mean follow-up time for the patients was 36.4 ± 12.3 (range, 24-72) months. The mean of union 3.3 ± 1.8 months. The HHS scores of the patients were excellent-good in 55.4% of patients, fair in 36% and poor in %8 of patients in this study. The mean HHS for all of the patients was 77.2 ± 10.2.

The SF-36 scores of the patients were evaluated for 3 health parameters and 8 sub-parameters. The mean scores in patients group were calculated as physical function 33.6 ± 24.9, physical role 23.6 ± 27.9, bodily pain 63.8 ± 21.5, general health 44.9 ± 17.4, vitality 36.8 ± 19.2, mental health 57.5 ± 15.2, emotional role 43.9 ± 39.1, and social function 56.8 ± 24.1. The mean SF-36 scores in patients and control group are shown in Fig. 2.

In the comparison of the SF-36 sub-parameters, the QoL of the patient group was observed to be lower than that of the control group in respect to physical function, physical role, vitality, and social function ($p < 0.001$, $p < 0.001$, $p = 0.032$, $p = 0.045$, respectively). The 3 health parameters, physical health, general health, and mental health were significantly lower in the patient group than in the control group ($p < 0.05$). The SF-36 data for both groups are shown in Table 2.

Table 1. Demographic data of the patients and the control group

	Elderly Hip Fractures (n = 103)	Control Group (n = 100)	*p* value
Age (years), mean±SD (range)	75.2±12 (65-93)	73.4±10.3	0.765
Gender			
Male	38	35	0.346
Female	65	65	
Side			
Right	54		
Left	49		
AO 31A classification			
Type 1	50		
Type 2	40		
Type 3	13		
Charlson comorbidity index, mean±SD (range)	4.4±2.1 (1-7)	4.1 ± 1.9 (1-6)	0.612
Mean of union time (months), mean±SD	3.3 ± 1.8		
Harris hip score, mean±SD	77.2 ± 10.2		

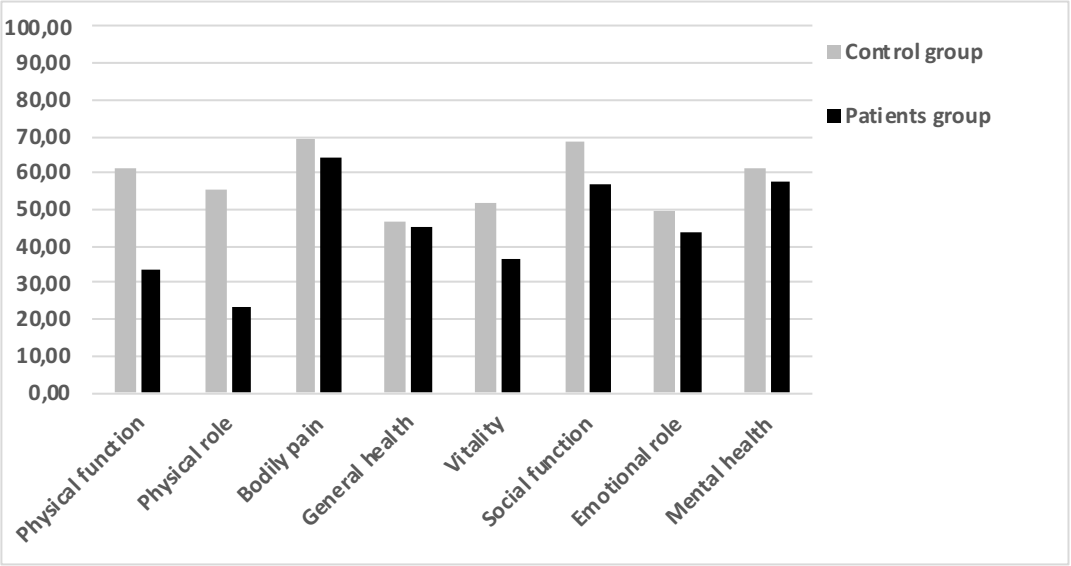

Fig. 2. SF-36 subtype-parameter data for the patients and control groups.

DISCUSSION

Non-union is a rare problem (1-2%) following pertrochanteric fractures, and generally successful HHS points are obtained with surgical treatment at a high rate (85-90%) [17]. Nevertheless, higher union rates and higher hip scores do not mean that the patients are completely healed. Thus, in addition to obtaining a bony union, the main aim should be regaining independent mobility and improvement of QoL. The surgical outcomes (HHS) of the current study were favorable in most cases; however, the QoL of the patients had not improved. The changes in physical, general, and mental QoL were examined in patients who obtained high hip scores and then compared with a normative population. In this study, the values for physical function, social function, and vitality in the elderly with hip fractures were significantly reduced compared to the control group. Moreover, even if the fracture had healed, QoL related to physical and social functions was not improved accordingly.

QoL questionnaires can be generic or disease-specific. Examples of generic questionnaires are the Nottingham Health Profile, the Sickness Impact Profile (SIP), Short Form 36 of the Medical Outcomes Study (SF-36), and the EuroQol (EQ-5D) [14, 18]. The SF-36 was published by Ware and Sherbourne, and selects 8 areas of health from a list of 40, in collaboration with the RAND Corporation [14]. This evaluation of 36 items of 8 subtypes consists of physical function (10 items), social function (2 items), physical role difficulty (4 items), emotional role (3 items), mental health

Table 2. Comparison of the SF-36 subtype-parameter data from the patients and the control group

	Elderly Hip Fracture	Control Group	*p* value
Physical function	33.5 ± 24.9	61.2 ± 24.9	**0.000**
Physical role	23.6 ± 27.9	55.5 ± 27.9	**0.000**
Bodily pain	63.8 ± 21.5	69.1 ± 21.5	0.231
General health	44.9 ± 17.4	46.4 ± 17.4	0.710
Vitality	36.8 ± 19.2	52.1 ± 19.2	**0.032**
Social function	56.8 ± 24.1	68.8 ± 24.1	**0.045**
Emotional role	43.9 ± 39.1	49.9 ± 39.1	0.344
Mental health	57.5 ± 15.2	61.1 ± 15.2	0.634

(5 items), energy/vitality (4 items), pain (2 items), and perception of general health (5 items). Reliability studies have been conducted for the Turkish version of the SF-36, and the Cronbach alpha coefficients were calculated for each subscale [19].

Musculoskeletal system diseases such as lower extremity arthritis, lumbar pathologies, and spinal deformities in the elderly could diminish the QoL of patients because they often lead to immobilization. Hellberg *et al*. [20] reported that hip and vertebral osteoporotic fractures can cause a decrease in predicted QoL while upper extremity osteoporotic fractures found not to be related decreased QoL. Rohde *et al*. [18] examined the impact of hip fractures on health-related and global QoL and they observed a significant decrease in the QoL. They emphasized the importance of the prevention of hip fractures [18]. Peterson *et al*. [10] observed a decrease in the physical role in a 1-year evaluation of 38 hip fracture patients. While this study did not use a control group for comparison, the return to previous physical activity level rate was reduced, and a significant change was observed in other SF-36 parameters [10]. In a study reporting the first year SF-36 scores of 62 hip fracture patients by Giessauf *et al*. [11], 63% of the patients had excellent or good results. However, they observed an increased bodily pain, and diminished social functioning, and mental health subscales and two summary scores (physical and mental component of SF-36) [11]. The absence of QoL of patients prior to the fracture makes it challenging to compare QoL values. Furthermore, retrospective scoring was not recommended if the national SF-36 was used or there was no control group [21]. A strong aspect of the current study was the selection of the control group from the same social region, matched demographic data of the patient group.

Koval *et al*. [22] showed that the type of fracture surgery was not a major factor affecting the healing but the age (> 85 years) of the patient and the pre-fracture mobility capacity were the important factors. Fox *et al*. [23] found that mobility prior to discharge, prolonged hospital stay, age, and male gender were directly influence the healing of hip fractures. In the same study, prolonged hospital stay was also shown to cause wound infections and pressure ulcers. In the current study, risk groups for poor results were not evaluated [23].

Limitations

There are some limitations of the current study. Negative factors that affect QoL were not evaluated, and therefore further research is required. Furthermore, a prospective study would be more enlightening, by acknowledging the difficulty in obtaining the pre-fracture status of the patients. Future studies could make a more systematic evaluation of elderly patients by making comparisons with other musculoskeletal system diseases.

CONCLUSION

In conclusion, the results of this study showed that the physical, social, and vitality parameters of patients with hip fractures was lower than control group; thus, negatively affecting their QoL despite successful surgery. New healthcare policies should be developed for these patients considering their physical capacity may not be fully regained. In addition, this study has demonstrated the importance of taking precautions to prevent hip fractures before the need arises for the treatment of hip fractures in elderly patients.

Authors' Contribution

Study Conception: YUY, MCO; Study Design: YUY; Supervision: EÖ; Funding: EÖ; Materials: YUY, AA; Data Collection and/or Processing YUY, MCO; Statistical Analysis and/or Data Interpretation: YUY; Literature Review: İD; Manuscript Preparation: YUY and Critical Review: MA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2022;8(1):31-36 Original Article

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The response to double-dose hepatitis B vaccination in patients with HIV

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ABSTRACT

Objectives: Prevention of hepatitis B virus (HBV) infection is necessary for patients with human immunodeficiency virus (HIV), since co-infection is associated with increased in mortality. The aim of this study was to investigate response to double-dose HBV vaccine in patients with HIV.

Methods: A total of 149 patients with HIV were retrospectively evaluated. Sixty-eight patients who were HBV seronegative and administered double-dose HBV vaccine were included in the study. According to anti HBs levels, patients were evaluated in three groups: < 10 mIU/mL, 10-100 mIU/mL and ≥ 100 mIU/mL. Age, sex, transmission route, smoking, alcohol-substance abuse, comorbidities, CD4+ T cells counts and HIV viral load were compared in three groups.

Results: The rate of response to HBV vaccination (anti HBs ≥ 10 mIU/mL) was 69.1%. Age was statistically significantly higher in the anti HBs < 100 mIU/mL group than in the anti HBs >100 mIU/mL group. The level of anti HBs was statistically significantly lower in patients with a CD4+ T cell count < 200 cells/μL (< 100 mIU/mL).

Conclusions: The use of high-dose vaccine is a necessity as well as revaccination to improve vaccine immunogenicity in patients with HIV. In our study, low CD4+ T lymphocyte count and older age were found to have a negative effect on vaccine response.

Keywords: HIV, HBV, co-infection, HBV vaccination, response

Patients with human immunodeficiency virus (HIV) infection are frequently coinfected with hepatitis B virus (HBV) because routes of transmission are shared [1]. Some 30%-90% of patients with HIV have serologic finding of previous HBV infection, and 10% have CHB infection. Co-infection with HIV and HBV was associated with an eight-fold increase in mortality compared with HIV monoinfection [2]. Therefore, prevention of HBV infection and HBV vaccination are necessary for patients with HIV. However, response rates to standard hepatitis B vaccination for patients with HIV are 24%-56%, compared with > 90% for immunocompetent hosts [3, 4].

The response to the HBV vaccine is influenced by the CD4+ T cell count and level of viral load. According to international guidelines; in patients with low CD4+ T lymphocyte counts (< 200 cells/μL) and high viral load, antiretroviral treatment (ART) should be initiated before HBV vaccination [5]. In patients who are HIV positive and who were vaccinated for HBV

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and do not respond [hepatitis B surface antibody (anti HBs) < 10 IU/L], revaccination should be considered. Double dose (40 µg) at 3-4 time points (0, 1, 6, and 12 mounts) may help to increase response rates to the HBV vaccine [5, 6].

The aim of this study was to investigate the rate of response to double-dose HBV vaccine and to compare the affecting factors to response in patients with HIV.

METHODS

The local ethics committee in Izmir Tepecik Training and Research Hospital approved the study. The study was designed as retrospective, observational. A total of 149 patients who were admitted to Tepecik Training and Research Hospital HIV/AIDS outpatient clinic between 2004 and 2017 and who were aged over 18 years and were HIV positive were evaluated for this study. Patients who were not adherent and were not followed up regularly (n = 20), who had natural immunity against HBV (n = 32), a previous response with HBV vaccine (n = 12), those who were HBsAg positive (n = 4) and, isolated hepatitis B core antigen (anti HBc) IgG positive (n = 13) were excluded from the study. Sixty-eight patients who were HBV seronegative (HBsAg negative, anti HBs negative, anti HBc IgG negative) were included in the study.

The patients' age, sex, HIV transmission route, smoking and alcohol-substance abuse status, comorbid diseases, CD4+ T cells counts and, viral load (HIV RNA) levels were recorded to assess the impact on vaccine response. HBsAg, anti HBc IgG and antiHBs results were tested by on enzyme-linked immunosorbent assay (ELISA) (Liason, Diasorin Diagnostic Specialist S.T.A., Italy). After evaluation of viral load, CD4+ T lymphocyte count and hepatitis markers in patients, vaccination and antiretroviral therapy (ART) were started simultaneously for HBV-sensitive patients.

Double-dose (40 µg) hepatitis B vaccine [hepatitis B virus surface antigen (HBsAg) (recombinant) 20 µg / 1 dose (1 mL) of Euvax (BERK)] was administered to 68 patients who were HBV seronegative at 0, 1 and 6 months. AntiHBs levels were assessed 6-8 weeks after the last vaccine. According to the antiHBs levels, patients were evaluated in 3 groups: < 10 mIU/mL (Group 1), 10-100 mIU/mL (Group 2) ve and ≥ 100 mIU/mL (Group 3). Those with an antiHBs level < 10 mIU/mL were considered as non-responsive to the first vaccination. Patients who did not respond to the first vaccination program were again vaccinated with double-dose (40 µg) hepatitis B vaccine at 0, 1, and 6 months.

Statistical Analysis

The data were evaluated using the IBM SPSS Statistics 22.0 statistical package program (IBM Corp., Armonk, New York, USA). Descriptive statistics are given as unit number (n), percentage (%), mean ± standard deviation (SD), median and interquartile range (IQR). Pearson's Chi-square test and Fisher's exact test were used to evaluate the categorical variables. The normal distribution of the numerical variables was evaluated using the Shapiro-Wilk test, the normality test, and Q-Q graphs. The independent sample t-test was used to compare two groups with normal distribution and the Mann-Whitney U test was used for groups with the non-normal distribution. In the comparison of three or more groups, one-way analysis variance (ANOVA) was used for normally distributed variables, and Kruskal-Wallis analysis was used for non-normally distributied variables. In multiple comparisons, Tukey's honestly significant difference (HSD) test was used for normal dividing variables and Dunn-Bonferroni test was used for normal non-dividing variables. A p value of < 0.05 was considered statistically significant.

RESULTS

The HBV serology of total 149 patients with HIV was evaluated (Table 1). The mean age of the patients was 52 (range,19-85) years. One hundred twenty-four patients (83.2%) were male. In the study, 37.98% (n = 49) patients with HIV had evidence of prior HBV infection, and 3.10% (n = 4) had chronic infection (HBsAg seropositive). At 0, 1, and 6 months, double-dose (40 µg) recombinant HBV vaccine was administered in all HBV-seronegative patients with HIV. Antibody levels were assessed at 6-8 weeks after the end of the vaccination programme. According to the anti HBs levels, 21 patients with < 10 mIU/mL (Group 1), 22 patients with 10-100 mIU/mL (Group 2), and 25 patients with ≥ 100 mIU/mL (Group 3) were iden-

Table 1. HBV serology in patients with HIV

HBV serology	Patients number n (%)
HbsAg (+)	4 (3.10)
Immunity against HBV infection HbsAg (-), AntiHBs (+), antiHbcIgG (+)	32 (24.80)
Isolated anti HBcIgG (+) HBsAg (-), Ant iHBs (-), antiHbcIgG (+)	13 (10.07)
Previously response of HBV vaccine HBsAg(-), Anti HBs (+), antiHbcIgG (-)	12 (9.30)
Seronegative HBsAg (-), anti HBs (-), anti HBcIgG (-)	68 (52.71)
Unfollow-up patients	20 (13.42)
All patients	149 (100)

tified. A total of 47 patients (69.1%) with anti HBs titers ≥ 10 mIU/mL were evaluated as vaccinated.

Ten of 21 patients who did not respond to the vaccine (anti HBs titers < 10 mIU/mL) received a double-dose of 0, 1, 6. month (40 µg) hepatitis B vaccination program second time. In three of these patients (30%), a response to the vaccine was achieved. The response to HBV vaccination in patients with HIV is shown in Table 2.

Age, sex, HIV transmission route, smoking-alcohol-substance abuse, comorbidities, CD4+ T cells counts, and HIV viral load results are shown in Table 3.

The age factor was statistically significant between group 1 and 2 and between group 1 and 3. (respectively $p = 0.038$, $p = 0.022$).

In patients with CD4+ T lymphocyte counts < 200 cells/µL, the level of antiHBs was found to be significantly lower (< 100 mIU/mL) than in patients with more than 200 cells/uL. ($p = 0.045$). Response of antiHBs antibody according to CD4+ The T lymphocyte counts are shown in Table 4.

In this study, age and CD4+ T cell counts were found significant factors in terms of response to hepatitis B vaccination in patients with HIV ($p < 0.05$).

Table 2. Response to HBV vaccination in patients with HIV

Vaccinated patients (n)	68
Responders, n (%)	47 (69.11)
Non-responders, n (%)	21 (30.88)
Vaccinated patients at second times (n)	10
Responders, n (%)	3 (30.00)
Non-reponders, n (%)	7 (70.00)
Non vaccinated patients at second times (n)	11

DISCUSSION

HIV affects the course of HBV infection negatively. HBV infection is a vaccine-preventable disease and although hepatitis B vaccination has a lower response rate, all HIV-infected patients are recommended to be vaccinated [7-10].

The risk of chronicity for HBV infection increases in patients with HIV who are HBSAg positive. Chronic hepatitis B (CHB) infection is around 5-10% in patients with HIV. Co-infected patients have a higher progression to cirrhosis and liver cancer and higher mortality than patients with a monoinfection. [6, 11, 12].

With the development of highly active antiretroviral treatment (HAART) and with better survival rates, liver disease has become a leading cause of mortality and is of great concern in co-infected patients with HIV-HBV. The incidence of acute HBV infection is lower among such patients than in patients infected with HBV alone however chronic HBV infection occurs more often [13-15]. In our study, 37.98% (n = 49) of patients with HIV had evidence of prior HBV infection, and 3.1% (n = 4) had chronic infections (HbsAg seropositive). The seropositivity rate of HBsAg in the patients with HIV was lower than in the literature [2, 11]. In addition, 9.3% of our patients were pre-vaccinated. Routine vaccination started in 1998 in our country and therefore these findings in the study were thought to be related to the predominance of the middle age group.

The effect of the vaccination program in Turkey that initiated in 1998 was observed decrease of HBsAg seroprevalence over time. In a previous review, HBsAg seroprevalence in Turkey was reported to be between 2.5-9%. This rate is 3.1% in patients with HIV. In another multi-center study, HBsAg seroprevalence was reported as 6.2% in HIV patients. In a study

Table 3. Anti HBs levels according to risk factors

Anti HBs levels	< 10 mIU/mL	10-100 mIU/mL	≥ 100 mIU/mL	*p value*
Patients (n)	21	22	25	
Age (years)*	46.45 ± 14.749[a]	47.09 ± 18.163[b]	35.56 ± 9.648[c]	**ac = 0.038 bc = 0.022**
Male gender	17	15	20	0.536
MSM	6	4	8	0.960
CD4 counts**	435 (410.75)	504.5 (562.75)	629 (602.5)	0.580
Viral load**	75500 (265650)	79838 (140499.5)	61700 (102550)	0.900
Smokers	12	12	12	0.722
Alcohol users	8	8	10	0.960
Narcotic drug users	3	1	2	0.485
DM	1	1	1	0,986
Comorbidities	5	6	5	0.841

*Mean ± standard deviation, **Median (IQR), MSM: Men who have sex with men, DM = Diabetes mellitus

Table 4. Response of anti HBs antibody according to CD4+ T lymphocyte counts

		CD+ T lymphosyties counts (cells/µl)		Total
		< 200	**≥ 200**	
AntiHBs (mIU/mL)	**< 100**	13	30	43
	≥1 00	2	23	25
Total		14	53	68

p = 0.045

by Inci *et al*., HBsAg positivity was 4.4%; exposure to hepatitis B (antiHBc IgG) was 34%. [16-18]. All these data point to the risk of co-infection in patients with HIV and emphasize the importance of vaccination in newly diagnosed young adults.

In general, symptomatic HIV-infected patients have suboptimal immunologic responses to vaccines. The antibody response to the antigen used in HBV vaccines, HBsAg, has been previously shown to be T-cell dependent, to induce a suboptimal antibody titer more frequently in HIV-positive individuals, and to more rapidly decline to non-protective levels than in HIV-negative controls [19].

In international guidelines, vaccination is preferably recommended after suppressed viremia and immune reconstitution (CD4+ T cell counts > 200 /µL). It is recommended to measure anti-HBs titers to evaluate their efficacy because vaccine responses can be significantly lower in patients with HIV [5]. Data on vaccination in isolated anti HBc IgG positive patients are not sufficient. For this reason, there is no clear recommendation for these patients. In patients at risk for HBV, if antibody response does not develop after HBV vaccination, annual HBV serology should be followed [5]. ART regimens containing tenofovir alafenamide or tenofovir disoproxil fumarate (TAF/TDF) are recommended for these patients. Revaccination is recommended until reaching anti HBs antibodies of ≥10 mIU/mL / ≥100 IU/L according to national guidelines [5]. In particular, in patients with low CD4 count and high viral load, who do not respond to HBV vaccine, double-dose (40 µg) vaccination is recommended 3 times if the antibody level is under 10 mIU / mL and once if it is under 100 mIU / mL [5]. In our study, the vaccine response was 30% in patients who were did not respond to the first vaccination program (anti HBs < 10 mIU/mL) and these patients were then vaccinated for a second time.

Response to HBV vaccine achieves in 80-90% of healthy adults. Antibody level > 10 mIU/mL is considered unresponsive. Antibody levels > 100 IU/L are regarded as ideal [20]. Age over 40 years, male sex,

obesity, hemodialysis, smoking, and being immunocompromised, including through HIV infection are factors that reduce responses to HBV vaccination [6]. After standard vaccination in patients with HIV, response rates to the vaccine range from 7% to 88% and are strongly correlated with CD4 cell numbers and viral load [23-29]. To improve the vaccine response, it is recommended that non-responders be re-vaccinated and use of higher and more frequent vaccine doses when viral load is suppressed with ART and CD4 + T lymphocyte counts are > 350-500 cells/μL [25-29].

In a systematic review and meta-analysis of five studies including a total of 883 patients, anti HBs response with high-dose (40μg) vs. standard-dose (20 or 10μg depending on vaccine type) vaccination were compared. It was observed that high dose vaccination increased the response rates [28]. In an open-label, multicenter, randomized study of patients with CD4 + T lymphocyte count > 200 cells/μL, three HBV vaccination strategies were evaluated. Three standard dose (20 μg) intramuscular administrations at 0, 1, and 6 months, four high-dose (40 μg) intramuscular administrations at 0, 1, 2, and 6 months, and four low-dose (4 μg) intradermal administrations at 0, 1, 2, and 6 months were compared. The response rates in patients were found 65%, 82%, 77%, respectively [28]. In another a cohort study authors reported that anti HBs response rates were 83% and 91% after three and four double-doses, respectively, and anti HBs levels were higher with the four-dose schedule [30]. In these studies, high-dose vaccination has been shown to increase response rates in nonresponders [28-30].

The main aim of this study was to investigate the results of high-dose vaccination and re-vaccination of non-responders to increase the HBV vaccine response in patients with HIV. There are similar studies in the literature. However, in our study, it is noteworthy that the double-dose vaccine was effective even though the patients had a high viral load. We think this is the reason for the initiation of ART in all patients. In addition, low CD4+ T lymphocyte count and older age were found to have a negative effect on vaccine response as in other studies. The rate of re-vaccination response was found as 30% in our study. These results also support the recommendations for re-vaccination in the guidelines.

CONCLUSION

In conclusion, the double-dose vaccination response in patients with HIV was consistent with the literature in this study. The use of high-dose vaccine is a necessity, as well as revaccination to improve vaccine immunogenicity in immunocompromised patients with HIV. The factors affecting response were found as age and CD4+ T lymphocyte counts, which were significantly different in the groups with anti HBs levels < 100 mIU/mL and ≥ 100 mIU/mL.

Authors' Contribution

Study Conception: MT, ŞK; Study Design: MT, TTK, SA; Supervision: MT, SA, ŞK; Funding: MT; Materials: MT, TTK; Data Collection and/or Processing: MT, TTK; Statistical Analysis and/or Data Interpretation: MT, TTK, SA; Literature Review: MT, SA; Manuscript Preparation: MT, TTK and Critical Review: MT, SA, ŞK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Rubella immunity in native Turkish and Syrian immigrant pregnant women between 2010-2018

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ABSTRACT

Objectives: The study has aimed to investigate the rubella immunity in native-Turkish and Syrian-immigrant pregnant women in Turkey.

Methods: Between September 2010 and December 2018, the hospital records of pregnant patients were evaluated retrospectively. For each year, for the number of patients who were screened for rubella IgG and/or IgM antibodies, IgG avidity (if any), and PCR tests (if any) were investigated, and subjects were categorized by nationality.

Results: During the study period, a total of 80,302 pregnant were tested with at least one of the rubella IgM or IgG antibodies. Of these, 22,962 pregnant women were screened for both IgG and IgM, 24,684 were screened for IgG, and 78,580 pregnant women were screened for IgM rubella antibodies. The seropositivity rate of IgG rubella antibodies in native and Syrian pregnant groups was 93.8% and 95.9%, respectively. In both groups, the IgM rubella antibodies were found as 0.5%. IgG avidity was investigated in 252 patients, whose test results were positive for IgM and IgG; and a low IgG avidity was detected in 5 native patients, while none was detected in the Syrian group.

Conclusions: In the Syrian immigrant group, the susceptibility to Rubella is low, and it does not differ from the native Turkish population.

Keywords: Rubella, seroprevalence, pregnancy, Syrian immigrant, vaccine

The Rubella disease is also called as German measles, and it is an infection caused by the Rubella virus, which is a single-stranded RNA virus of the Togaviridae family [1]. Rubella virus is transmitted from person to person through the respiratory tract. The disease is generally seen during childhood, and in most cases, it is experienced as a mild, self-limiting disease. In the symptomatic cases, the general symptom of the disease is maculopapular rashes, accompanied by fever, fatigue, and lymphadenopathy [2]. But in some cases, especially in post-pubertal women, it can be more serious, causing arthritis and arthralgia, rarely encephalitis, and thrombocytopenic purpura [1, 3].

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The disease possesses an extra risk in pregnant woman, because it can be transmitted from an infected mother to the fetus by the transplacental way, which may result in the congenital rubella syndrome (CRS) in the fetus [1, 3]. The CRS is associated with multiple anomalies such as cataracts, glaucoma, chorioretinitis, microphthalmia, and hearing loss; brain anomalies such as microcephaly, pulmonary artery stenosis; heart anomalies such as ventricular septal defects; as well as miscarriages and fetal deaths. In the surviving cases, long-term complications like serious hearing loss, the risk of developmental delay, autism, thyroiditis, and insulin-dependent diabetes (type 1 diabetes) can be seen [1].

Vaccination is considered the most effective method to prevent rubella spread and CRS. The World Health Organization (WHO) in 2014, published the global immunization report that 140 countries have already introduced rubella vaccine into their routine immunization program [4]. In 1970, Rubella vaccination was started, especially in rural areas in Turkey. National Expanded Immunization Program (EIP) started in 1981 with the starting of the Measles and Rubella Elimination and the Prevention of Congenital Rubella Syndrome Program with the rubella infection prevention campaign; and it continued after triple measles, mumps, and rubella (MMR) vaccine applications in 2006 [5]. As a result, almost all the children born in Turkey have received two doses of rubella-containing vaccine. Consequently, the number of rubella cases during pregnancy and CRS cases have decreased over time with childhood vaccinations. The eliminating of the CRS cannot be achieved only by vaccination of children; in addition, susceptible women at childbearing age must be identified, and if possible, must be immunized for rubella at least three months before conception.

Due to the outbreak of the war that took place in Syria, the national health system of the country collapsed, and most people did not have a chance to access the vaccines. After migration due to the war, the vaccination status became too dependent on the migrated countries' vaccination services to the migrants. Turkey has hosted the highest number of Syrian immigrants over time, especially after the year 2011 [6]. There has been great concern about the susceptibility of the Syrian pregnant women because of the reasons mentioned above. The investigation of the rubella susceptibility rates of both native Turkey and immigrant women is essential to preventing rubella and congenital rubella. Nonetheless, there are a few articles on the rates and comparison of rubella immunity among native mothers and Syrian immigrant mothers. Accordingly, the present study has aimed to investigate the rubella immunity among native and immigrant pregnant women in Turkey.

METHODS

Subjects

Between September 2010 and December 2018, a total of 80,302 patients, who were screened for at least one of the IgM or IgG rubella antibodies, were included in this retrospective cohort study. This study was approved by the Medical Specialty Education Board of the Etlik Zübeyde Hanım Women's Health Practices and Research Center, Decision Number: 90057706-799. According to our clinical routine, all pregnant patients who applied to the hospital for prenatal care were screened for rubella disease or seropositivity. For the patients with only the rubella IgG antibody positivity, further tests were not performed because these patients had been immunized to rubella. For the patients with only rubella IgM antibody positivity, the test was repeated after 2 weeks, and if the result of the test was negative, then the first result was accepted as a false positive; but if the result of the test was reported as positive again, then these patients were closely followed up for acute rubella disease. For the patients whose serum rubella IgG and IgM antibodies were both positive, serum IgG avidity was investigated [7]. Patients with low IgG avidity were determined as an acute infection, and further evaluations such as PCR study of chorionic villus sample, amniocentesis, or cordocentesis are performed [8-11]. The patients' nationality, age, test results of IgM and IgG rubella antibodies, IgG avidity (if any), and PCR (if any) was retrieved from the hospital database and patients' files. The patients were evaluated according to the first pregnancy or birth records of the patients in our hospital. Repeated results were excluded from the study.

Serological Tests of Anti-rubella IgG and IgM

Rubella IgG and Rubella IgM tests were studied

from the erum samples using chemiluminescence method on the Liaison brand device of Diasorin Company (DiaSorin, Saluggia, Italy), between 2010 and 2013; and on "Advia Centavur XP (Siemens Diagnostics, Tarrytown, NY) device from Siemens, between 2014-2018, in line with the recommendation of the device manufacturers. Rubella IgG Avidity test was performed with the Microelisa method from serum samples by the manufacturer's recommendations with the Euroimmun brand kit (Euroimmun, Lübeck, Germany).

Statistical Analysis

IBM SPSS Statistics version 21.0 for Windows was used to calculate the variables. Descriptive analysis and categorical variables were defined as numbers and percentages, and numerical variables were defined as median (range minimum-maximum) values. For the comparison of total seropositivity between nationals, a Chi-Square test was performed.

RESULTS

During the study period, rubella antibody tests were performed on a total of 80,302 pregnant women, including IgM for 78,580 patients, IgG for 24,684 patients, and both IgM and IgG for 22,962 patients. The median age of all the tested patients was 32 (16-49). A total of 1,590 Syrian pregnant women were evaluated in the study. The number of Syrian pregnant women who applied to our center for prenatal care was

Table 1. Prenatal rubella screening results between September 2010-December 2018

Year	Nationality	Number (n) of the Patients	Age	IgM-	IgM+	IgG-	IgG+	Avidity		
			Median (Min-Max)	n	n (%)	n	n (%)	Total	High	Low
2010	Turkish	2.765	34 (23-49)	2.649	13 (0.5)	49	841 (94.5)	8	8	0
	Syria	5	37 (33-41)	5	0 (0)	1	0 (0)	0	0	0
2011	Turkish	8.602	34 (21-47)	8.234	80 (1)	142	2.304 (94.2)	17	17	0
	Syria	19	37 (28-47)	18	0 (0)	0	8 (100)	0	0	0
2012	Turkish	9.026	33 (22-47)	8.779	36 (0.4)	91	1.377 (93.8)	36	35	1
	Syria	21	35 (27-48)	21	0 (0)	0	3 (100)	0	0	0
2013	Turkish	9.010	32 (21-47)	8.683	69 (0.8)	229	2.450 (91.5)	19	19	0
	Syria	16	32 (24-42)	16	0 (0)	0	5 (100)	0	0	0
2014	Turkish	8.756	31 (19-47)	8.567	49 (0.6)	93	1.925 (95.4)	23	23	0
	Syria	19	32 (26-46)	19	0 (0)	0	7 (100)	0	0	0
2015	Turkish	10.166	31 (18-47)	9.976	59 (0.6)	27	2.406 (98.9)	31	31	0
	Syria	155	29 (16-48)	152	1 (0.7)	0	35 (100)	1	1	0
2016	Turkish	10.932	30 (18-49)	10.694	40 (0.4)	58	3.078 (98.2)	53	51	2
	Syria	262	28 (18-44)	259	1 (0.4)	6	105 (94.6)	1	1	0
2017	Turkish	10.408	29 (18-47)	10.203	35 (0.3)	40	3.755 (98.9)	42	40	2
	Syria	469	27 (18-45)	452	1 (0.2)	6	194 (97)	1	1	0
2018	Turkish	9.047	28 (18-47)	8.824	34 (0.4)	73	4.907 (98.5)	20	20	0
	Syria	624	26 (18-46)	607	4 (0.7)	17	352 (95.4)	0	0	0
2010-2018	Turkish	78.712 (98%)	32 (18-49)	76.609	415 (0.5)	802	23.143 (93.8)	249	244	5
	Syria	1.590 (2%)	32 (16-48)	1.549	7 (0.5)	30	709 (95.9)	3	3	0
p value			0.92	0.631			0.292			

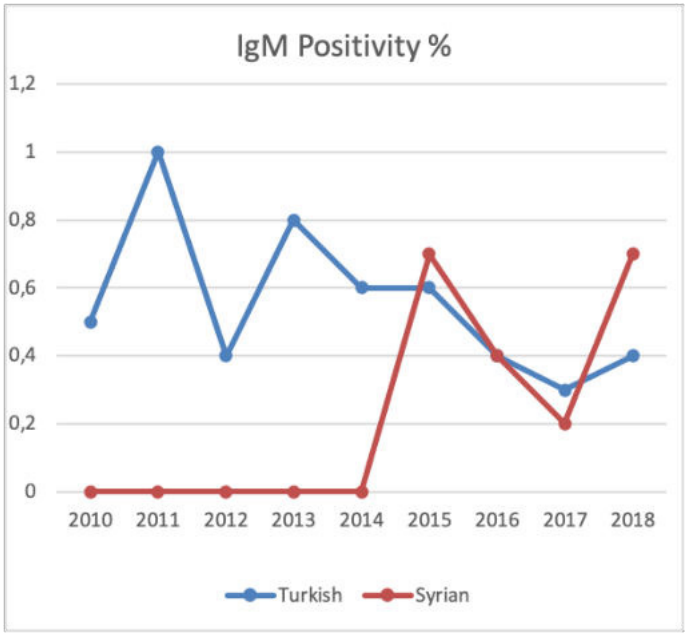

Fig. 1. Graphic of IgM posivity

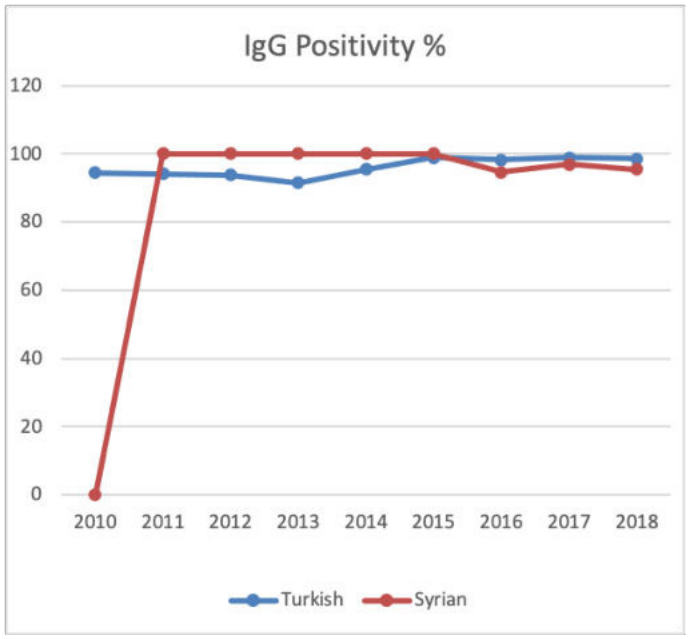

Fig. 2. Graphic of IgG positivity.

in an increasing trend each year (Table 1). The results of the native Turkish and Syrian immigrant pregnant woman were similar in respect to having serum rubella IgG antibodies and rubella IgM antibodies. Hence, the rate of rubella IgG antibodies positivity were 93.8% and 95.9%; and the rate of rubella IgM antibodies positivity were 0.5% and 0.5%, respectively (p = 0.292, p = 0.631) (Table 1). Rubella IgM ve IgG positivity results have been presented for the years of 2010-2018, in Fig. 1 and 2. IgG avidity was investigated in 252 patients, whose test results were positive for both rubella IgM and IgG antibodies. A low IgG avidity was detected in 5 patients, and all of them were in the native pregnant group. The results of the two pregnant women, who were negative for amniocentesis and the PCR, is shown in Table 2.

DISCUSSION

Due to the migration wave in 2011, which took place from Syria to other countries (especially to Turkey), there has been an increase in the incidence of vaccine-preventable diseases [12, 13]. One of these diseases, which is the subject of this study, has been thought to be rubella disease. Overall, we observed that the rubella susceptibility and seropositivity rates between native Turkish pregnant women and Syrian immigrant pregnant women were similar. In this study, the rubella susceptibility rates in Syrian groups were found to be in the range from 0% to 5.4%, and in native groups, it was 1.1% to 8.5%, according to years. Rubella IgG seroprevalence can vary even in different regions in the same country [4, 8, 14, 15]. The studies

Table 2. Characteristics of patients with low IgG avidity

Age	Gravidity	Parity	Test week	Nationality	Ultrasound finding	Pregnancy result	PCR result	Birth week
43	7	2	9	Turkish	Normal	Abort	-	-
36	3	2	8	Turkish	Normal	Birth	Negative[a]	39
20	1	0	5	Turkish	Normal	Birth	-	40
27	2	1	14	Turkish	Echogenic focus in the liver and intestine	Birth	Negative[a]	38
34	7	3	8	Turkish	Normal	Birth	-	39

[a] Amniocentesis result

from different areas of Turkey showed that the rate of susceptibility to rubella in native pregnant women ranged from 2.5% to 17%, and IgG seropositivity ranged from 83.69 to 97.5% [16-18]. There is a limited number of studies conducted on Syrian refugees in Turkey for the susceptibility of rubella, and according to one of these studies, which had results that were similar to this study, 1333 Syrian pregnant woman were evaluated, and the IgG seropositivity was found to be 92.8% [19]. The current study evaluated the data of groups between September 2011 and December 2018. In the first years of the migration, the population of Syrian immigrants in Ankara was low. The reason for including the data between 2011 and 2014 was to see the progress of the Syrian immigration application over the years, which we saw increasing from year to year.

Despite all efforts to eradicate rubella, in some areas, the disease is still prevalent, and it is a significant, preventable cause of fetal death, abortion, congenital anomaly, and birth defects [20, 21]. The American College of Obstetricians and Gynecologists suggests a routine screening for rubella in pregnant women [22]. Similar to Turkey, many countries such as The United Kingdom, Japan, and Canada have implemented this strategy into regular obstetrics care, and good performance has been achieved [23, 24]. Via this strategy, necessary measures can be taken during pregnancy, and postpartum vaccination can be completed to reduce the risk of congenital rubella for a subsequent pregnancy [22].

Although the studies for the attenuated rubella vaccine started in 1965, its effective use started in 1978 with the incentive of the Federal Childhood Immunization Program and Measles Elimination Initiative [25]. As of 2018, the rubella vaccine has entered the vaccination programs in 168 countries around the world, and rubella transmission has not been observed in 81 of these countries since that time[24]. Congenital rubella syndrome and rubella infection were prevented in 3 out of 6 WHO regions, and the Global Vaccine Action Plan and WHO plans to increase this to 5 WHO regions by 2020 [26, 27]. The Centers for Disease Control and Prevention suggests two doses as the first dose applied in the 12th-15th month and the second dose applied in the 4-6th year after birth [28]. Two doses of triple MMR vaccine are administered in Turkey. According to WHO data, MMR is applied at 12 and 18 months after birth in the Syrian vaccination program [29].

The course and complications of rubella infection during pregnancy may differ depending on the gestational week. Before the 10th week, it can cause fetal defects, including pregnancy loss, in 85-90% of the infected patients, and rare fetal adverse effects are seen from the 16th week of gestation [30]. Rubella antibody screening at the first obstetric visit provides the chance for early diagnosis and early information about the course of the pregnancy. In the current study, a low IgG avidity was observed in 5 (%1.9) out of 252 patients with positive rubella IgG and IgM antibodies. Only 2 patients were accepted for the amniocentesis and PCR test, which both gave negative results for rubella infection. Two patients who refused both the amniocentesis and PCR test had healthy newborns without any complications. Over-demanding of the IgM antibody test by physicians over the IgG antibody test is due to the non-standardized prenatal screening routine among physicians.

The strength of the study is that the changes in the susceptibility of native and Syrian immigrant pregnant women were evaluated continuously for 8 years.

Limitations

There have been some limitations in our study. First, we collected the data of patients in a single regional center, which might not reflect the susceptibility of the rest of Turkey and Syrian immigrants who live in the other cities of Turkey. Secondly, immunization records of the immigrant women were not present, hence we could not explain how they became seropositive for rubella.

CONCLUSION

The outbreak of the war that took place in Syria, which resulted in the migration of 3.5 million people from Syrian to Turkey, caused great concern for outbreaks of infectious diseases such as rubella. This study showed that vaccination for rubella was successful for both the Syrian migrants and native pregnant women. It is thought that this success will continue in future generations with the vaccination policy implemented by Turkey for immigrants.

Authors' Contribution

Study Conception: ÖYÇ, AY; Study Design: ÖYÇ, AY, DŞ; Supervision: ÖYÇ, AY, DŞ; Funding: ÖYÇ; Materials: ÖYÇ; Data Collection and/or Processing: GA, MO, AK, MGÇ; Statistical Analysis and/or Data Interpretation: ÖYÇ, GD, AY, DŞ; Literature Review: ÖYÇ, AY, DŞ; Manuscript Preparation: ÖYÇ, MO, GD, AK, AY and Critical Review: ÖYÇ, AY, DŞ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Footwear alterations after first metatarsophalangeal joint arthrodesis

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ABSTRACT

Objectives: This study aimed to examine the footwear alterations following first metatarsophalangeal (MTP1) joint arthrodesis.

Methods: A retrospective review was performed on 37 (42 feet) patients who underwent MTP1 joint arthrodesis between January 2014 and January 2019 in our institution. Functional outcomes were assessed with the American Orthopedic Foot and Ankle Society Hallux metatarsophalangeal–interphalangeal (AOFAS-MTP-IP) scale, and the pain was assessed using the visual analog scale (VAS). Besides, time to return regular footwear, shoe preferences, the cosmetic appearance of the feet were evaluated and compared with preoperative status.

Results: The mean follow-up time was 12.0 ± 16.5 months. The preoperative AOFAS-MTP-IP scale improved from 46.6 ± 7.0 points to 86.2 ± 7.2 points (p = 0.001), and VAS decreased from 6.3 ± 1.8 points to 1.4 ± 0.5 points (p = 0.001). There was non-union in three (7.1%) feet, and the mean union time for the rest of the feet was 8.2 ± 1.1 weeks. No other complications were seen. The mean time for resuming regular footwear was 11.8 ± 2.6 weeks. Patients' perception of the appearance of their feet improved from 3.9 ± 2.8 to 9.0 ± 0.7 points (p = 0.001). Twenty-nine (78.6%) patients (33 feet) reported that there was no restriction in footwear compared to the past, but 8 (21.4%) patients had to choose specific types and models. None of the patients had to use modified or custom-made shoes. There was significant change in the heel height preferences after the surgery (p = 0.004). 18 (52.4%) patients had to choose shorter heel height than preoperative preferences, whereas 19 (47.6%) patients' preference did not change. Almost all patients, 36 (97.6%) were using athletic shoes in their routine daily life.

Conclusions: MTP1 joint arthrodesis is a reliable method that controls pain and increases function with a low rate of complications. However, significant alterations in footwear preferences may occur. Patients should be informed adequately about these outcomes to modify patient expectations.

Keywords: Hallux valgus, hallux rigidus, arthrodesis, footwear, outcome

First metatarsophalangeal (MTP1) joint arthrodesis is usually indicated in the end-stage osteoarthritis of the MTP1 joint that is refractory to conservative management, severe hallux valgus deformity more than 40° of hallux valgus angle (HVA), and salvage procedure after unsuccessful primary forefoot surgery [1, 2]. This procedure is an effective solution that controls pain and provides deformity correction with a

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low rate of complications [3]. However, MTP1 joint arthrodesis is a joint destructive procedure that completely restricts motion and eliminates the normal functions of the MTP1 joint. Consequently, gait and footwear alterations may occur [4, 5]. MTP1 joint plays a vital role in walking. At least 60 degrees of extension is required starting from heel-off to toe-off during a normal gait cycle. Moreover, it must be stable enough to carry the body weight and act as a lever for forward propulsion [6].

Previous studies on gait analysis following MTP1 joint arthrodesis have shown significant changes such as decreased power of push-off, cadence and decreased step length, deterioration in plantar pressure distribution, and load to lesser toes, and compensation of hindfoot and forefoot movements to restore normal gait [3-7]. All these adverse changes in the gait kinematics and foot biomechanics also affect footwear preferences and use. There are quite a limited number of studies examining how footwear has been altered after this procedure in the current literature [8, 9]. However, when informing patients about this surgery and obtaining consent, one of the questions frequently asked by patients is footwear changes [9]. Furthermore, footwear alterations have been shown to be closely associated with patient satisfaction in forefoot surgery [10].

The aim of this study is to examine the functional results after the MTP1 joint arthrodesis by focusing on the alterations of footwear.

METHODS

Study Design and Patients

A retrospective review was performed on digital medical records to identify all patients who underwent the first metatarsophalangeal joint (MTPJ) arthrodesis between January 2014 and January 2019 in our institution. The institutional patient database was used to collect all radiological imaging records in the Picture Archiving and Communication System (PACS), patient charts, operation reports, medical records, and the notes taken during follow-up visits. Patients with incomplete medical records, imaging files, and patients with less than one-year follow-up were excluded from the study.

During the time interval under study, a total of 52 patients were identified who underwent MTPJ arthrodesis. Of these, ten patients were lost in follow-up, three patients declined to participate, and two patients had improper medical and radiological records. Thus, 37 patients (42 feet) with a mean age of 58.6 ± 13.7 years (range, 20-74 years) were included in the final analysis. Indication of arthrodesis was hallux rigidus in 14 feet and hallux valgus in 28 feet. This research was performed in compliance with the ethical principles set out in the 1964 Helsinki Declaration and its later modifications, and the study protocol was approved by the institutional review board (Approval date and issue: 2020/033).

Surgical Technique and Postoperative Follow-up

Patients were operated on under spinal anesthesia and tourniquet control. A dorsomedial incision was made, and the superficial cutaneous nerve was dissected and protected. After capsulotomy, all osteophytes were removed; in hallux valgus cases, a bunionectomy was also performed if necessary. Removal of cartilage was performed down to subchondral cancellous bone using cup and cone reamers. The MTP1 joint was held in the desired arthrodesis position with a contemporary K wires fixation, and fluoroscopic control was made before definitive implantation. A dorsal MTP arthrodesis locking plate was used for the fixation, and additional interfragmentary screw fixation was used in 14 feet (Fig. 1). A short-leg plaster cast was applied to all the patients for

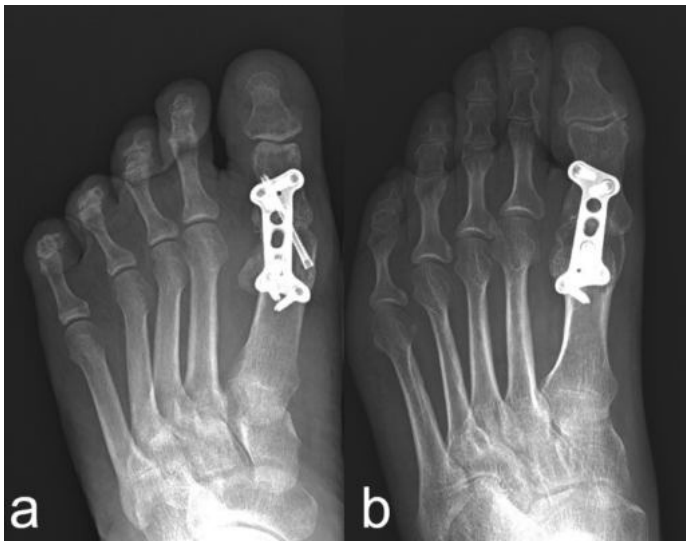

Fig. 1. (a) Dorsal plate with interfragmentary screw fixation (b) Single dorsal plate.

the first two weeks. At the end of the second week, the cast was removed, and the patient was encouraged weight-bearing as tolerated on the heel and lateral side of the foot while the patient was wearing stiff-soled shoes. After the detection of the radiographic and clinical bony union at follow-up, full weight-bearing with regular shoes was allowed.

Radiographic Evaluations

Hallux valgus angle (HVA) and the first and second intermetatarsal angle (IMA) were measured on preoperative and final follow-up radiographs. Measurements were taken according to the recommendations of the ad hoc committee of the American Orthopedic Foot and Ankle Society [11]. Coughlin and Shurnas classification was used for grading of hallux rigidus cases [12]. Union of arthrodesis was evaluated on serial follow-up radiographs, and bridging bone formation on at least three cortex and arthrodesis site was accepted as a union.

Clinical Evaluations

Functional outcomes were assessed with the American Orthopedic Foot and Ankle Society Hallux metatarsophalangeal–interphalangeal (AOFAS-MTP-IP) scale, and the pain was assessed using the visual analog scale (VAS) [13]. Preoperative and final follow-up scores were compared. In addition, a questionnaire was prepared to assess the effect of arthrodesis on footwear alterations (Table 1).

Statistical Analysis

Statistical analysis was performed using SPSS Statistics Base v.23 for Windows. Continuous variables were presented as mean ± standard deviation, median, and range. Categorical variables were stated as percentages and frequency distribution. The Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. Comparative analysis of dependent variables was performed using the Chi-square test for categorical variables, Wilcoxon Signed rank test for continuous variables in accordance with the normality testing. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

There were 37 patients (9 male, 28 female) with a mean age of 58.6 ± 13.7 years (range, 20-74 years).

Table 1. The questionnaire that was used for the assessment of footwear alteration after MTP1 joint arthrodesis

1. How many weeks did it take to start wearing regular footwear after the operation?									
2. What was your heel size preference before the operation?									
a. Up to 2 cm		b. Up to 4 cm		c. Up to 6 cm		d. More than 7 cm			
3. Currently, what heel size do you prefer for your comfort?									
a. Up to 2 cm		b. Up to 4 cm		c. Up to 6 cm		d. More than 7 cm			
4. Currently, could you choose your footwear without restriction?									
a. I can tolerate any kind of shoe without restriction.		b. I can tolerate only comfortable shoes; my footwear selection is partly restricted.		c. I cannot tolerate regular shoes, and I have to choose specific brands with high toe box shoes. My footwear selection is severely restricted.					
5. Which shoe type do you prefer in your daily life?									
a. Formal shoes		b. Casual shoes		c. Athletic shoes					
6. How would you score the appearance of your feet preoperatively on a scale 1-10, 1 being the poor and 10 being perfect?									
1	2	3	4	5	6	7	8	9	10
7. How would you score the appearance of your feet postoperatively on a scale of 1-10, 1 being the poor and 10 being perfect?									
1	2	3	4	5	6	7	8	9	10

Five patients had bilateral MTPJ arthrodesis; thus, 42 feet (24 right, 18 left) were analyzed. Preoperative diagnosis was hallux rigidus in 14 feet (4 Grade III and 10 Grade IV) and hallux valgus in 28 feet (HVA > 40° for all). A dorsal plate was used in 14 feet, and a dorsal plate with an additional interfragmentary compression screw was used in 28 feet.

The mean follow-up time was 12.0 ± 16.5 months (range, 12-72 months). The preoperative AOFAS-MTP-IP scale improved from 46.6 ± 7.0 points to 86.2 ± 7.2 points (p = 0.001), and VAS decreased from 6.3 ± 1.8 points to 1.4 ± 0.5 points (p = 0.001). There was non-union in three (7.1%) feet, and the mean union time for the rest of the feet was 8.2 ± 1.1 weeks (range, 6-12 weeks) (Fig. 2). No other complications were seen. Computerized tomography was performed in non-union cases, and it revealed fibrous type non-union in two cases without loss of position, and there was a loss of position in one patient with failure of implants (Fig. 3). Although revision surgery was offered, all denied a secondary intervention.

The mean time for resuming regular footwear was 11.8 ± 2.6 weeks (range, 8-20 weeks). Patients' perception on the appearance of their feet improved from 3.9 ± 2.8 (range, 1- 8) to 9.0 ± 0.7 (range, 8-10) points (p = 0.001). Twenty-nine (78.6 %) patients (33 feet) reported that there was no restriction in the selection of footwear compared to the past, but 8 (21.4 %) patients (9 feet) had to choose specific types and models. None of the patients had to use modified or custom-made shoes with complete restriction. There was a significant change in the heel height preferences after the surgery (p = 0.004) (Table 2). Eighteen (22 feet, 52.4%) patients had to choose shorter heel height compared to preoperative preferences, whereas 19 patients' (20 feet, 47.6%) preference did not change. Almost all patients, 36 (41 feet, 97.6%) were using athletic shoes in their daily life.

DISCUSSION

The current study examined the functional outcomes and footwear alterations after the MTP1 joint arthrodesis. Results of this study showed that functional outcomes were significantly improved compared to preoperative period and the pain was adequately decreased. Subjective rating on the appearance of the foot was also improved. No major complication was seen except nonunion in three feet. In this respect, MTP1 joint arthrodesis is a safe and reliable treatment for end-stage hallux rigidus and severe hallux valgus cases.

However, half of the patients switched to wear shoes with less heel height than they used to. In the other half, there was no change in heel selection, but none of the patients could wear high-heel shoes (over 7 cm) before surgery. One out of five patients reported

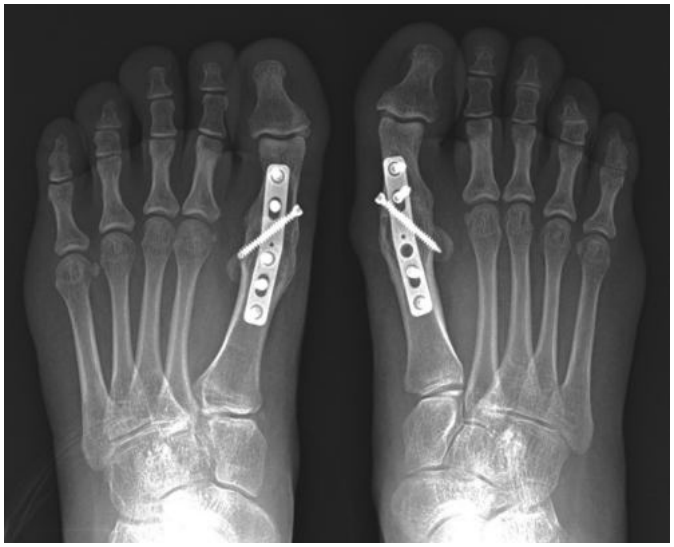

Fig. 2. Radiographic results of a patients with dorsal plate ad interfragmentary screw fixation at the final followed. Complete bony consolidation was seen.

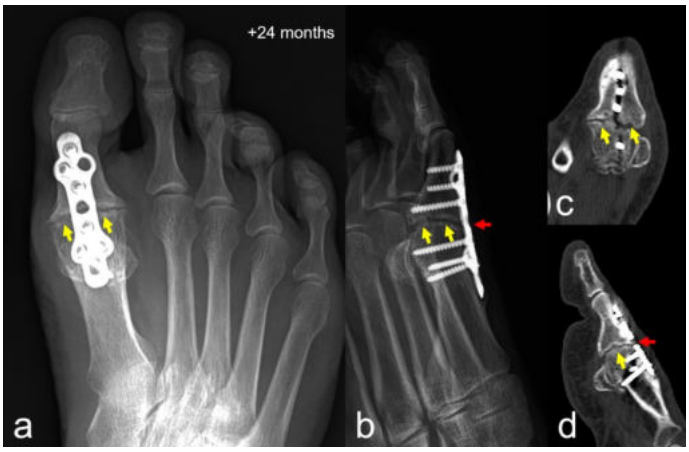

Fig. 3. Anteroposterior (a), and lateral (b) foot radiographs showing nonunion (yellow arrows) and failure of the dorsal plate (red arrow). Axial (c) and sagittal (d) computerized tomography demonstrate fibrous nonunion (yellow arrows) and discontinuity of the dorsal plate (red arrow).

Table 2. Summary of results

Variable	Preoperative	Postopoperative	*p*-value
AOFAS (points ±SD)	46.6 ± 7.0	86.2 ± 7.2	**0.001**
VAS (points ±SD)	6.3 ± 1.8	1.4 ± 0.5	**0.001**
Appearance of Feet (points ±SD)	3.9 ± 2.8	9.0 ± 0.7	**0.001**
Heel Size Preference (n)			**0.004**
Up to 2cm	9	22	
Up to 4cm	23	20	
Up to 6cm	10	0	

that they had to prefer certain shoe models for their comfort. Almost all patients reported to choose athletic shoe models in their routine daily life. In the light of these findings, it can be said that MTP1 joint arthrosis significantly alters the footwear preferences of the patients.

Shoes have emerged as a protective garment that facilitates walking in the outdoor environment and reduces injury, but has become a social theme. It is one of the most important components of fashion. It is also an indicator of socio-cultural status. Therefore, freedom in footwear preference is a factor that increases quality of life. In a recent study that conducted on large number of patients who underwent forefoot surgery, wearable range of shoes was reported as the one of the three factors that influence the final patient satisfaction [10]. DeSandis *et al*. [8] reported that 79% of the patients were limited to wearing comfort shoes only following MTP1 joint arthrodesis. Our findings are consistent with these results. Consequently, it is necessary to provide detailed information on the footwear alterations following this procedure at the time of consultation. Alternative treatment methods should be considered in patients with high expectations or those who do not accept these alterations. Osteotomies that preserve joint movements, resection or interposition arthroplasty, and implant arthroplasty might be better option for these patients.

Limitations

The most obvious shortcoming of this study was retrospective data collection on small group of patients. Secondly, both hallux valgus and hallux rigidus cases were included although same procedure was per formed to all patients.

CONCLUSION

In conclusion, MTP1 arthrodesis is a reliable solution end-stage hallux rigidus and selected hallux valgus cases. However, significant footwear alterations might occur, such as wearing flat and athletic shoes. Surgeons should explain these issues in detail to modify patient expectations.

Authors' Contribution

Study Conception: HM, MÜ; Study Design: GG, ÖK; Supervision: ÖK; Funding: HM; Materials: HM; Data Collection and/or Processing: HM, YAK; Statistical Analysis and/or Data Interpretation: MÜ; Literature Review: MÜ, GG; Manuscript Preparation: HM and Critical Review: YAK, ÖK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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Validity and reliability study of the vaccine hesitancy scale in Turkish sample

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ABSTRACT

Objectives: This study aims to test the validity and reliability of the Vaccine Hesitancy Scale (VHS) developed by Larson for Turkish society due to the limited measures of vaccine hesitancy studies in Turkey. This scale can help advance research and vaccination policy for human well-being.

Methods: Two hundred fourty-six participants completed the first questionnaire in Turkish between September and October 2020. The sample of the study was determined to consider the number of items on the 9-item scale is more than 27 times. The retest was used to test the validity of the scale in the study.

Results: The ratio of the scale to chi-square degrees of freedom is 2.29. This can be considered as a sufficient fit. As a result of the first level Confirmatory Factor Analysis (CFA), the values of the goodness of fit suggested that the two-factor model can be considered compatible with the data. The Cronbach's alpha of the total items of the scale is = .801. Factor 1 which was the 'lack of confidence' of Cronbach's alpha was 0.904. Factor 2 that was the 'risks' was 0.742. The reliability and validity of the VHS analysis revealed a two-factor structure with construct and criterion validity to detect vaccine hesitancy.

Conclusions: VHS is recommended to be used as a data collection tool in health care services to detect the level of vaccine hesitancy among the public. The adaptation of VHS into the Turkish language can help health care providers and immunization policy makers to improve effective approaches by focusing on the individuals' confidence in vaccination.

Keywords: Confidence in vaccination, vaccine hesitancy, scale, vaccine

Vaccine immunization is undoubtedly the best cost-effective method of combating preventable diseases of the last century [1]. The vaccine provides both individual and social immunization [2]. Vaccination programs are the most effective method that has been used to prevent and eliminate communicable diseases and reduce morbidity and mortality rates for public health [1]. According to the report of the WHO (2019); global immunization prevents 2-3 million deaths in a year. The global immunization rate has been around 85% for the last few years. It is stated that the vaccination can prevent 1.5 million more people from deaths per year by increasing the immunization rates to the targeted level [3].

When the vaccination was first introduced in Europe in the 18th century to prevent smallpox, people had started to hold hesitancy about vaccination [4-6]. "Vaccination hesitant" mean delayed acceptance or re-

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fusal of vaccination despite the availability of services [7]. Vaccine hesitancy was defined as attitudes such as anxiety or doubts as well as a behavior [8]. Factors contributing to vaccine hesitancy are different based on the specific vaccine, individual factors, social influences, and environmental conditions [9, 10]. For example, there are different attitudes around vaccine hesitancy related to the distrusting vaccines or healthcare providers and different perceptions of the need for vaccination [11, 12].

WHO (2019) identified vaccine hesitancy as an important issue that can solve ten global health problems. Importantly, it plans to resolve in recognizing the importance of community immunization and the increase in vaccine-preventable diseases. WHO has proposed a multifaced strategy to reduce and stop individuals' vaccine hesitancy by developing vaccination programs to proactively prevent vaccine hesitations in many countries [3]. In the last 20 years, especially in the last 8 years, concerns against vaccination and vaccine hesitancy have started to increase again, and WHO established the "Vaccine Hesitancy Working Group" in 2012 and began to investigate the reasons for vaccine rejection [13]. This research group developed a measure to explore vaccine hesitancy through a systematic review of existing research, a review of questions used by the WHO and UNICEF Joint Reporting Form, and expert consultation [14]. WHO recommended to implementing these tools to evaluate and research in different contexts to determine whether they can be used as a basis for measuring vaccine hesitancy. Moreover, they focused on how this can be adapted to low- and middle-income countries [13]. In response to this recommendation, one of these tools with the potential to measure and compare vaccine hesitancy across countries and overtime was the Vaccine Hesitancy Scale (VHS). This tool has been approved and evaluated in Canada, Guatemala, and more recently in the United Kingdom and Sudan [15-18]. Findings from these four countries revealed that VHS is a valid and reliable tool for measuring vaccine hesitancy. Also, it was recommended that VHS needs further adaptation and validation in different contexts [15-18]. The development and standardization of a vaccine hesitancy measure are crucial to improving jurisdiction and the ability to measure, evaluate and compare over time.

The development and standardization of a vaccine hesitancy measure are key to improve jurisdiction and the ability to measure, evaluate and compare over time. Recently, several scholars also paid attention to the COVID-19 vaccine hesitancy as a public health problem [19-23]. Therefore, the VHS can be used to examine the level of vaccine hesitancy during the COVID-19 crisis. Importantly, there are no existing tools for measuring vaccine hesitancy in Turkey. The examination of the vaccination hesitancy has been started by using different measures at the international level. Some of these measures are the 8-item Vaccine Confidence Scale [24], 18-item Parental Attitudes towards Childhood Vaccination Scale [25], 7-Item Vaccination Conspiracy Belief Scale [26], 12-item Vaccination Attitudes Review Scale [27], 5-item Vaccine Attitude Scale [28]. Larson *et al*. [14] tried to standardize the vaccine hesitancy measure. These studies help us to recognize the importance of examining the vaccine hesitancy to improve confidence in vaccination. Insufficient quality of the data prevented the monitoring of various indicators. While vaccine hesitancy is an important public health problem, the measures around vaccine hesitancy have been limited to cover the complexity of confidence in the vaccination process [3]. A standardized, validated measurement tool of vaccine hesitancy will help develop the research and immunization policy. This tool has the potential to widely use to explore the relationship between vaccine instability, vaccine hesitancy and vaccine coverage, compare vaccine hesitancy between countries. Also, it can evaluate how individuals' vaccine hesitancy can change over time. This article aims to adapt the Vaccine Hesitancy Scale developed by Larson *et al*. [14] to Turkish society and examine whether it is a valid and reliable measurement tool in the adult sample.

METHODS

Considering the lack of reliable and valid measures around vaccine hesitancy in Turkey, this article tested the validity and reliability of the VHS in the Turkish language. The VHS was developed by Larson *et al*. [14] and tested the validity and reliability by Shapiro *et al*. [16]. This study examined the structure and internal consistency of the scale, construct validity, and criterion validity. We used an online survey to

test the reliability and validity of VHS in Turkish language. The participants who were recruited through social media (e.g., Instagram, Facebook, WhatsApp, Twitter etc.) lived in Turkey. The data were collected through applications on the web between October and November 2020. The inclusion criteria were (i) accepting to participate in the research, (ii) being over 18 years old, and (iii) being able to read and write. Data were collected by random sampling method. The sample of the study was more than 27 times the number of items on the 9-item scale, and 246 participants completed the first questionnaire. It is also stated that the sample size should be five or even ten times the number of observed variables [29, 30]. For the calculation of the reliability coefficients, the Re-test method, which is the application of a measurement tool to the same subject group twice in the same conditions and at a certain time interval, was used [29, 30]. Fifteen days after the first questionnaire, the same questionnaire was sent to the participants again for re-test. Seventy-two participants completed the re-test part. Research data were collected by using the Participant Information Form and the VHS.

Ethical Considerations

Bartın University Ethics Committee Approval was obtained to collect research data (2020-SBB-0204-22/08.10.2020). The first question of the online form was about consent regarding whether or not the person agreed to participate in the study. In this way, participants read the information about the study and give consent for participation in the study. Participants who gave their consent were included in the study.

Data Collection Tools

Participant Information Form

The authors prepared this form to explore the participants' socio-demographics. These socio-demographic items were about age, educational status, marital status, the number of children, etc.

Vaccine Hesitation Scale

This scale was developed by Larson *et al*. [14] to examine vaccine hesitancy, attitudes and problems regarding vaccination. Shapiro *et al*. [16] found that VHS has two factors with construct and criterion validity in determining parents who are hesitant about vaccination. In this study, Shapiro *et al*. [16] tried to verify the nine-item VHS Likert-type scale question that was validated. The scale consists of 9 questions and two sub-dimensions: lack of confidence and risks. Items 1, 2, 3, 4, 5, 6, 7 are included in the lack of confidence dimension of the scale and items 8, 9 are included in the dimension of the risks. Scale questions are reverse coded up to 1-7. The scale has a five-point Likert-type rating included five points: "1-strongly disagree; 2-disagree; 3-neither agree nor disagree; 4-agree; "5-strongly agree". As the seven items were reversed, the higher score indicates more vaccine hesitancy. Scores range from 9 to 45 for the total number of sub-groups. The Cronbach alpha coefficient for the "lack of confidence" sub-dimension of the original scale was 0.90 and the "risks" was 0.64.

Statistical Analysis

Frequency, standard deviation, and item mean were performed to assess the data revealed from the VHS. Pearson correlation analysis for item analysis was used to test the reliability. Cronbach's alpha analysis for internal consistency of the total scale and its sub-dimensions was implemented. Also, test-retest scores for time invariance were compared. SPSS version 22 and Amos version 24 programs were used for the analysis.

RESULTS

Sample Characteristics

The sample consisted of 62.2% female, 37.8% male participants. Their educational status was 52.8% undergraduate, 17.5% primary education, 15.4% graduate and 14.2% high school level. The average age of the participants was 36.47 ± 37.43 years, and the average monthly income of the family was 6.056.36 ± 6.946.97 Turkish Liras. It was determined that 65.4% of the participants were married and 61.4% had children. 58.9% of participants heard negative information about vaccines.

The Validity of the Vaccine Hesitation Scale

Translation Procedures

Permissions of adopting the scale in the Turkish language were obtained via e-mail from Heidi J. Larson who is the original developer of the scale and Gilla K. Shapiro who psychometrically evaluated it. The

original scale was translated from English to Turkish by three faculty members from the departments of Social Work, Psychology and Public Health, who have mastered both English and Turkish languages, are native speakers of Turkish. Three translated versions were compared by the authors and the researchers developed a common Turkish text from these three Turkish translations. The linguists compared the scale that became original. The study started after the linguists gave congruence.

Content Validity

The opinions of 20 experts were taken to evaluate the compatibility of the scale, which was translated into Turkish, with our culture and language. The profession of these experts included public health (including one professor, 3 associate professors and 4 assistant professors) and midwifery (including a professor, 3 associate professors and 4 assistant professors). However, no feedback was received from four faculty members. The expert team was informed about the study process and requested to evaluate 9 questions regarding the suitability of the question contents, the status of meeting the area to be measured, the scope and language validity.

Based on the technique developed by Lawshe [31], the qualitative data obtained following expert opinions were converted into quantitative data after calculating the SVS and SVI values to determine the content validity and language validity of the items to be included in the scale. The content validity of the study was 0.91 and the language validity SVI value was 0.80. The fact that the SGI value obtained is greater than the SVI value (SGI > SVI) indicates that the content validity of the remaining items in the scale is statistically significant [31, 32]. The Kaiser Meyer Olkin (KMO) value of VHS was 0.862. The normal range of KMO value indicates that the explanatory factor analysis results can be applied to the data. As a result of the Bartlett Sphericity test, there was a significantly high correlation between variables and the data that means suitable for explanatory factor analysis (X2: 1156.115, SD: 36, $p < 0.001$).

Reliability Analyzes

First, exploratory factor analysis (EFA) was performed in the study. According to EFA results, there are six items in the first factor and three items in the second factor. It was seen that the 5th item, which was located under the first factor in the original scale, was located under the second factor differently in the Turkish version of the scale. The eigenvalue of VHS's lack

Table 1. Distribution correlation of the items of the Vaccine Hesitation Scale by sub-dimensions

Items	Lack of confidence sub-dimension	Risk sub-dimension
1. Childhood vaccines are important for my child's health	0.82	
2. Getting vaccines is a good way to protect my child/children from disease	0.90	
3. Childhood vaccines are effective	0.86	
4. Having my child vaccinated is important for the health of others in my community	0.86	
5. All childhood vaccines offered by the government program in my community are beneficial		0.77
6. The information I receive about vaccines from the vaccine program is reliable and trustworthy	0.74	
7. Generally, I do what my doctor or health care provider recommends about vaccines for my child/children	0.75	
8. New vaccines carry more risks than older vaccines		0.82
9. I am concerned about serious adverse effects of vaccines		0.84
Eigenvalue	4.25	1.92
Explained Variance Total (68.69%)	46.22%	22.46%
Cronbach's alpha	0.904	0.742

of trust sub-dimension was 4.25 and the variance was 46.22%; the eigenvalue of the risk sub-dimension was 1.92 and the variance was 22.46%. The total variance explained is 68.69% (Table 1). It would be possible that the items of the scale, which consists of nine items, are distributed in a balanced way. One of the positive features of the scale is that the number of items distributed among the factors is not less than three [33].

To achieve the item-total score correlation; it is recommended that the sample size should be at least 100-200 people or at least 5 people should answer for each item [34]. If the item-total score correlation coefficient is 0.30 and above, its reliability is considered to be good [34, 35]. (see Table 1). In the lack of confidence sub-dimension of the scale, the item correlation coefficient was between 0.74 and 0.90. In the lower height of the risks, the coefficient was between 0.77-0.84. Therefore, the reliability of the scale was found to be good.

The internal consistency coefficient was examined for the reliability of VHS. For this, the Cronbach Alpha Coefficient was first measured. Cronbach's alpha for the instrument was .801 for the total scale. Cronbach's alpha for Factor 1 was .904 and Factor 2 was 0.742 (Table 1). If the Cronbach Alpha Coefficient is 0.60-0.80, it is highly reliable, and 0.80-1.00 indicates high reliability [36]. Lack of confidence sub-dimension of internal consistency coefficients of VHS was high reliability, and the risks sub-dimension were found quite reliable.

Structure Validity

CFA was performed to evaluate the validity of the one-factor structure of the VHS, which consists of two sub-dimensions and a total of 9 items in the Turkish sample group. The results obtained in the first construct validity analysis were found sufficient. The scale illustrates 68.69% of the variance with this form. The first level factorial structure of VHS (6-item lack of confidence and 3-item risk factor structure), which consists of two sub-dimensions and a total of 9 items. This is presented in Fig. 1. As a result of CFA, the goodness of fit values of the scale obtained (x2 (26, n = 246) 91.75; $p < 0.008$; x2/df = 2.290; CMIN = 59.534; the root mean square error of approximation (RMSEA) = 0.073; the comparative fit index (CFI) = .97; the goodness of fit index (GFI) = .92) and two-factor shows that the model can be considered compatible with the data. These results show that the data obtained from the research are compatible with the predicted institutional structure of VHS (two-factor

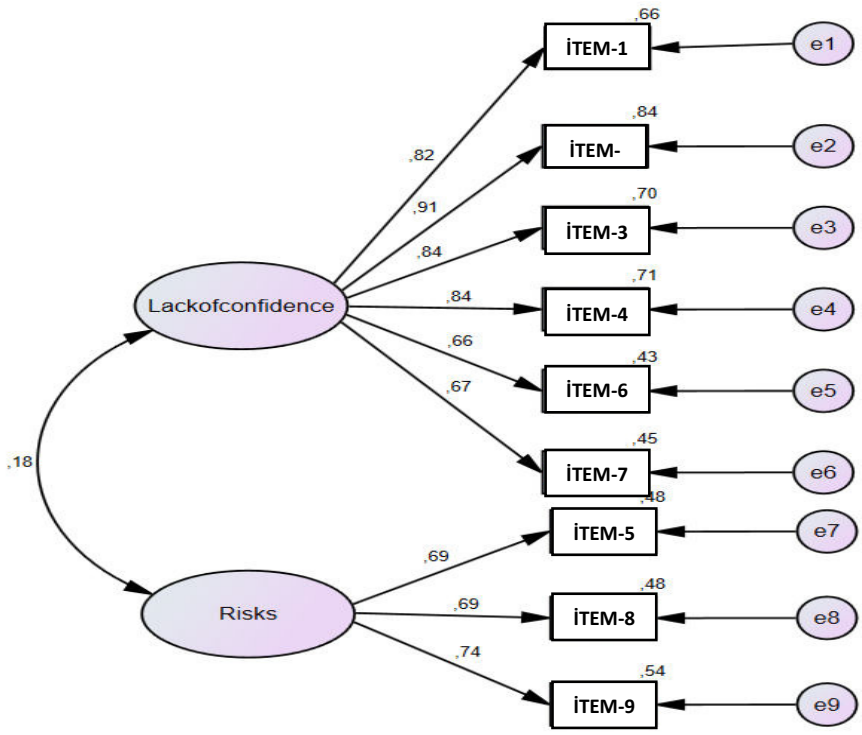

Fig. 1. First level factorial structure of the Vaccine Hesitation Scale.

Table 2. Standard regression coefficients of the Vaccine Hesitation Scale

Scale items	Standard Regression Coefficients		
	Lack of confidence sub-dimension	Risk sub-dimension	
VHS -1	0.82		
VHS -2	0.91		
VHS -3	0.84		
VHS -4	0.84		
VHS -5		0.69	
VHS -6	0.66		
VHS -7	0.67		
VHS -8		0.69	
VHS -9		0.74	
Fit indices	**Good fit**	**Acceptable fit**	**Scale values**
χ^2/df	$0 \leq \chi^2/sd \leq 2$	$2 \leq \chi^2/sd \leq 5$	2.290
***p* value**	$0.05 < p \leq 1.00$	$0.01 < p \leq 0.05$	**< 0.001**
RMSEA	$0 \leq RMSEA \leq 0.05$	$0.05 \leq RMSEA \leq 1.0$	0.073
NFI	$0.95 \leq NFI \leq 1.0$	$0.90 \leq NFI \leq 0.95$	0.949
CFI	$0.95 \leq CFI \leq 1.0$	$0.90 \leq CFI \leq 0.95$	0.971
GFI	$0.95 \leq GFI \leq 1.0$	$0.90 \leq GFI \leq 0.95$	0.925

CFI = the comparative fit index, GFI = the goodness of fit index, NFI = the normed fit index, RMSEA = the root mean square error of approximation, VHS = Vaccine Hesitation Scale

model). As seen in Table 2, the acceptable fit of x^2/df, RMSEA, the normed fit index (NFI) and GFI values show a good fit of CFI values. As a result of the analyzes, it can be interpreted that the original structure of the scale with two factors is compatible with Turkish culture. In the standard regression coefficient analysis of VHS items and scale sub-dimensions, "lack of confidence" was found between 0.66-0.91, and the "risks" sub-group was found 0.69-0.74. The 9-item form obtained to measure the VHS retest reliability was sent again fifteen days later and 76 people responded. Pearson's correlation coefficients were calculated and it was found that the correlations found were significant.

DISCUSSION

This study examined the psychometric properties of the "Vaccine Hesitancy Scale" that adapted to Turkish. Shapiro *et al*. [16] calculated the common variance of the 10-item scale as 66.73%, and the 9-item English version as 57.25. Also, Luyten *et al*. [37] used the English version and determined that the scale consisting of two factors and 9 items explained 71.8% of the total variance . Sabahelzain *et al*. [18] observed that the two-factor structure of the 10-item version of the scale made up 50.8% of the total variance in the study of adapting the scale to the Saudi language. This study was found that the scale consisting of two factors and a total of 9 items constituted 68.69% of the total variance. It is similar to the studies done with VHS.

In the confirmatory factor analysis, analyzes were performed for two factors of 9 items of the scale. It clearly showed the best fit in the analysis results. Thus, a two-factor structure consisting of a 6-item 'lack of confidence' section and a three-item 'risks' section

showed the best psychometric properties of VHS. The study by Shapiro *et al*. [16] found that confirmatory factor analysis was performed for both 9 and 10-item versions of the scale and both one and two-factor solutions, and clearly showed the best fit for the two-factor 9-item version (RMSEA = 0.0750, CFI = 0.9, TLI = 09666). Similarly, we found that the 9-item version showed the best goodness of fit. Many studies also found that CFA complies well [16, 18, 37].

Shapiro *et al*. [16] removed item 10, a nine-item VHS was divided into two factors, seven and two, respectively. In their study, the first factor (consisting of seven items) represents 'lack of confidence' and the second sub-dimension (consisting of two items) represents 'risks'. In the study, as a result of the explanatory factor analysis in 9 items of VHS, a two-factor structure with VHS subscales characterized by 'lack of confidence' and 'risks' was revealed. The first subdimension (consisting of six items) represents “lack of confidence” and the second sub-dimension (consisting of three items) represents “risks”. Therefore, the 5th item was distributed under the risk subgroup. CFA analysis results in this direction showed good harmony. Domek *et al*. [15] stated that there are five items loaded on the first factor in his study, and these are primarily related to vaccine trust and positive attitude towards vaccines. There were two items loaded into the second sub-dimension regarding vaccination risk and peace of mind, and perceptions that vaccines are not beneficial. However, items in each subscale were loaded differently from other studies, because in our study, the 'lack of confidence' subscale consisted of 6 items and the risks subscale had 3 items. Shapiro *et al*. [16] stated that for the future development of the scale, the number of items in the 'risks' component should be increased. Generally, fewer than three items of the factors are considered unstable, and the Cronbach α calculation has limitations for a two-item subscale [38]. The risks subscale of the scale should consist of 3 items. These differences were due to the adaptation of the scale [15-17]. Vaccine hesitancy is a complex and multidimensional issue [16, 25, 39]. Similarly, with other studies, [16, 32, 37]. our findings suggest that our adaptation is far from one-dimensional VHS. It showed that it makes it very two-dimensional because trust and risk structures have been recognized as part of vaccine hesitation.

The Cronbach alpha for the VHS total scale in the study was 0.80. The Cronbach alpha for the first subdimension 'lack of confidence' was .90 and the second sub-dimension 'risks' was 0.74. In the study by Shapiro *et al*. [16], Cronbach's was α 0.92 for 'lack of confidence' and Cronbach's α 0.64 for 'risks' . Domek *et al*. [15], Cronbach's alpha values for the confidence subscale and the peace of mind subscale were 0.78 and 0.70, respectively. Likewise, studies noted that Cronbach alpha values were higher [15]. The Cronbach alpha coefficient, which is a measure of the internal consistency of items, is used to explain or question the homogeneous structure of the items in the scale. It is interpreted that the items in the scale with a high Cronbach alpha coefficient consist of items that are consistent with each other and that measure the same feature. If the Cronbach alpha coefficient is 0.60-0.80, it is highly reliable, and 0.80-1.00 indicates that it is highly reliable [36]. The data of this study were found to be reliable.

The retest reliability of VHS shows that it measures the relevant structure properly. Also, a large correlation between VHS subscales and retest indicates that VHS has criterion validity. The fact that the subscale means were almost the same for the study group and the retest group supports the accuracy of the study in terms of both validity and reliability. Likewise, the findings of the two data groups in the lack of confidence and risks subscale are very close to each other. The parallelism of the averages in the study also shows the consistency of the findings in two different periods and provides evidence about the validity and reliability of the scale.

Vaccine hesitancy is complex and specific to the situation and varies with time, place and types of the vaccine. It is affected by factors such as indifference, comfort and trust [13]. Vaccine hesitancy is constant and it can be measured by evaluating attitudes and beliefs towards infectious diseases. The multifactorial and complex causes of the hesitancy around vaccination require a wide variety of approaches, interventions and policy changes. These changes also should be implemented at the individual, community, health system and national levels. Improving understanding of how these factors vary between different subpopulations among healthcare providers, the healthcare system and public health authorities can help the studies of vaccine hesitancy. Importantly, this scale can help us understand the individuals’ level of vaccine hesi-

tancy during the COVID-19 epidemic as this understanding can develop appropriate interventions. Therefore, standardized measurement tools such as those proposed by SAGE will make it easier to measure the amount of hesitancy. It is necessary to have the capacity to measure the geographic clustering of hesitancy. Changes in the prevalence of hesitancy over time through serial, cross-sectional questionnaires using standardized questions and methods are critical [20]. The fact that the findings obtained as a result of statistical analysis are quite compatible with the data in the original article of VHS shows the validity and reliability of the scale [16].

Limitations

The findings of the study should be interpreted within the geographical, socioeconomic and sociocultural context of the research participants and areas. Retest data were obtained by contacting the people in the study group after an average of 2 weeks. It was very difficult to reach even 76 people out of 246 as a repeat group.

CONCLUSION

Minimizing vaccine hesitancy is an international priority. VHS has been adapted and used in many countries, but these countries are generally in the United States of America and Europe. While there might have been cultural differences regarding the Turkish form of the scale at the beginning of the study, the data showed that VHS is quite compatible with Turkish culture. VHS has been found two factors including 'lack of confidence' and 'risks' with structure and criterion validity in identifying individuals with vaccine hesitancy. Shapiro *et al*. [16] evaluated the reliability of the retest and found it to be reliable. A standardized, validated measure of vaccine hesitancy beliefs will help advance the research and vaccination policy.

Authors' Contribution

Study Conception: HYD, İD, ZT; Study Design: HYD, İD, ZT; Supervision: HYD; Funding: HYD, İD, ZT; Materials: HYD; Data Collection and/or Processing: HYD, İD, ZT; Statistical Analysis and/or Data Interpretation: HYD, İD; Literature Review: HYD, İD, ZT; Manuscript Preparation: HYD, İD, ZT and Critical Review: HYD, İD, ZT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(1):59-64 Original Article

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Thiol/disulphide balance and ischemia modified albumin levels in relapsed brucellosis patients

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ABSTRACT

Objectives: In the study, it was aimed to determine the Thiol/Disulphide profile in patients with relapsed brucellosis and the relationship between Ischemia Modified Albumin (IMA) Levels and Thiol/Disulphide profile.

Methods: Native thiol, Total thiol, Disulphide, Disulphide/Native thiol, Disulphide/Total thiol, IMA levels were measured in forty patients with relapsed brucellosis and healthy control group by using the newly developed method in this cross-sectional study.

Results: There was no statistically significant difference in patients with relapse brucellosis despite the fact that it was lower than total thiol control group ($p > 0.05$). Disulphide was detected high in patients with brucellosis but no statistically significant difference was found ($p > 0.05$). Native thiol and total thiol ratios of disulphide were found to be statistically higher in patients with relapsed brucellosis ($p < 0.05$). In addition, the ratio of native thiol and native thiol to total thiol was statistically lower than the control group ($p < 0.05$). The levels of IMA were statistically significant in patients with relapsed brucellosis compared to the control group ($p < 0.05$). There was a statistically significant positive correlation between IMA values and Disulphide and Disulphide/Native thiol, Disulphide/Total thiol, Native thiol/Total thiol ratios (r = 0.514, r = 0.527, r = 0.527, r = 0.527; respectively).

Conclusions: It is known that the response of brucellosis treatment can be followed up with oxidative stress markers and it can also be used as a relapse indicator in our study.

Keywords: Relapse brucellosis, thiol/disulphide, ischemia modified albumin

Brucellosis is a zoonotic infectious disease that affects half a million people annually and is considered one of the most important problems for public health [1]. *Brucella* species can grow and survive in macrophages [2]. Oxidative explosion in host macrophages is the primary mechanism controlling intracellular replication of *brusella*. In addition, inhibitors of reactive oxygen species have been reported to reduce anti-*Brucella* activity of macrophages [3]. Therefore, oxidant-antioxidant molecules have been reported to have a very significant role in *Brucella* endurance and pathogenesis. It is reported that brusellosis may be associated with production of oxygen radicals and the emergence of antioxidant depletion,

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and that oxidative stress plays a role in the patogenesis of brusellosis [4].

Thiols are mercaptans based sulfhydryl residues that play a significant role in the coordination defense network [4]. In the case of oxidative stress, with the oxidation reaction of cysteine residues, thiols oxides and reversible disulfide bonds are formed. Disulphide bond can be reduced again to thiol group. In this way, thiol-disulphide homeostasis occurs [4]. In various diseases such as cerebral ischemia, pulmonary thromboembolism, coronary artery disease, preeclampsi, policystic over syndrome, celiac disease, impaired thiol disulfide balance has been demonstrated [5-8]. Inflammatory cells which get activated through the production of reactive oxygen and nitrogen compounds fight against microbial pathogens that are considered to be causative agents a variety of infectious diseases [9]. For this reason, Thiol-Disulphide homeostasis was evaluted in infectious diseas such as Crimean Kongo Hemorrhagic Fever and tonsillopharyngitis, and a shift to oxidative side of balance was indentified [10]. The ischemia modified albumin (IMA) results from the modification of cobalt binding sites from the N- terminal end of albumin with the emergence of free radicals in ischemic tissue [11]. This new albumin molecule, which has lost its ability to bind cobalt, has been reported to be an early marker of ischemia. Furthermore, the use of IMA as a marker for sepsis and community- acquired pneumonia associated with oxidative stress and ischemic damage has been reported in the literature [12, 13].

In our study, it was aimed to determine the relationship between thiol- disulphideprofile and IMA use as an oxidative stress indicator in patients with relapsed brucellosis.

METHODS

Study Population

This cross-sectional coverage consisted of 40 patients with relapsing disease and 40 healthy individuals who had been diagnosed with brucellosis within the last 6 months who applied to infectious diseases polyclinic. The age and gender of the control group were in agreement with the patient group. Those with known infections, inflammatory or chronic diseases and those who smoke or drink alcohol were excluded.

Definition

Brucella relaps, with or without bacteria, has been recognized as a recurrence of clinical symptoms within the past six months, with an additional increase in previously titrated Wright and 2- mercaptoethanol titers [14].

Sample Collection

Approval for study was taken from the local ethics committee (Erzurum Regional Training and Research Hospital – Clinical Research Ethics Committee 2016/12-110). Approval forms are signed for all illnesses and healthy control groups. Venous blood samples were collected between 8 and 10 o'clock in the morning after eight hours of fasting, was separated after centrifugation at 1500× g for 10 minutes andstored at -80°C before theanalysis.Thiol/Disulphide homeostasis parameters were quantified utilizing the new way developed by Erel and Neselioğlu [15]. C-reactive protein (CRP) levels were measured by nephelometric method (Siemens Dade Behring BN II).

Statistical Analysis

The data were entered into the SPSS 21.0 statistical package program and analyzed using the same package program. Categorical variable from the descriptive data were presented as frequency distributions, and percentile and continuous variables as mean (±) standard deviation and median (largest, smallest value). The normality of distribution of continuous variables was tested by Shapiro-Wilk test. The significance of differences between the groups was evaluated using Mann-Whitney U test, Student's t test, and variance analysis where appropriate and Chi-square and Fisher exact tests were used to examine the difference between categorical variables. Spearman correlation analysis was performed to evaluate the relationship between IMA and thioldisülfide parameters. The statistical significance value was accepted as $p < 0.05$.

RESULTS

Forty brucellosis patients and 40 healthy individuals were included in the study. There was no statistically significant difference between the age of the patients included in patient and control group. Demo-

graphic and laboratory data between the two groups were presented in Table 1. Relapsing brucellosis patients were found to have a significantly higher sedimentation value than healty control group.

No statistically significant difference was found in patients with brucellosis despite the low detection rate compared to the total thiol control group ($p > 0.05$). Disulphide was found high in patients with bru-

Table 1. Demographic characteristics and laboratory parameters of the study groups

	Brusellosis (n = 40)	Control group (n = 40)	*p* value
Age (year), median (min-max)	43 (16-75)	39.5 (18-74)	0.707
Gender (male/female)	19/21	15/25	0.131
CRP (mg/dL), median (min-max)	0.55 (0.20-16.00)	0.32 (0.32-1.98)	0.107
Sedimentation (mm/h), median (min-max)	14.0 (2.0-41.0)	5.5 (2.0-38.0)	**< 0.001**
Leukocyte count ($\times 10^3$/L), median (min-max)	6.65 (3.08-22.40)		
Platelet count ($\times 10^3$/L), median (min-max)	259 (95-537)		
ALT (U/L), median (min-max)	27.5 (10.0-133.0)		
AST (U/L), median (min-max)	24.5 (12.0-85.0)		
Creatinine (mg/dL), median (min-max)	0.73 (0.50-1.18)		
Hemoglobin (g/dL), median (min-max)	14.00 (9.40-18.10)		
Previous treatment, n (%)			
Rifampicin+doxycycline	37 (92.5)		
Rifampicin+doxycycline+ aminoglycoside	1 (2.5)		
Doxycycline+ quinolones	2 (5.0)		

CRP = C-reactive protein, ALT= Alanine aminotransferase, AST = Aspartate aminotransferase

Table 2. Thiol/disulfide profiles and ischemia-modified albumin levels of the study group

	Brusellosis (n = 40)	Control group (n = 40)	*p* value
IMA	78.05 (71.80-90.50)	75.90 (68.50-83.30)	**0.003**
Native thiol (µmol/L)	280.95 (126.70-414.00)	322.05 (211.50-390.90)	**0.028**
Total thiol (µmol/L)	332.35 (152.70-496.10)	347.45 (232.10-437.50)	0.214
Disulphide (µmol/L)	20.75 (0.80-43.60)	13.50 (0.35-30.85)	0.066
Disulphide/Nativethiol (%)	7.26 (0.22-15.96)	4.85 (0.14-10.58)	**0.009**
Disulphide/Total thiol (%)	6.34 (0.22-12.10)	4.42 (0.14-8.74)	**0.009**
Native thiol/Total thiol (%)	87.30 (75.80-99.56)	91.15 (82.53-99.72)	**0.009**

Data were expressed as median (minumum – maximum), IMA = Ischemia modified albumin,

Table 3. Relations between thiol-disulphide profiles and ischemia-modified albumin levels

	Native thiol	Total Thiol	Disulphide	Disulphide/ Native thiol	Disulphide/ Total thiol	Native thiol/ Total thiol	Sedimentation
IMA	r = 0.189	r = -0.65	**r=0.514**	**r =0.527**	**r =0.527**	**r =0.527**	r = 0.248
(n = 80)	***p* = 0.012**	*p* = 0.692	***p* = 0.001**	***p* < 0.001**	***p* < 0.001**	***p* < 0.001**	*p* = 0.123

IMA = Ischemia modified albumin

cellosis but no statistically significant difference was detected ($p > 0.05$). The native thiol and total thiol ratios of disulphide were statistically higher in patients with relapsed brucellosis ($p < 0.05$). In addition, the ratio of total thiole to native thiol and native thiol was statistically lower than the control group ($p < 0.05$). IMA levels were found statistically higher in patients with brucellosis than control group ($p < 0.05$) (Table 2). There was a statistically significant positive correlation between IMA value and Disulphide and Disulphide/Native Thiol, Disulphide / Total thiol, Native thiol/ Total thiol ratios ($p > 0.500$, $p < 0.05$) (Table 3).

DISCUSSION

Relaps of brucellosis occurs as an important problem during the treatment. Cellular immunity and treatments provided bacterial elimination; however, chronic and relapsed infections were seen due to the presence of intracellular microorganisms. Previously, *Brucella* –PCR was used for the detection of *Brucella* relapse [16]. In our study, it was aimed to determine the thiol/ disulphide profile in patients with relapsed brucellosis and, at the same time to determine the relationship between IMA levels and thiol/ disulfide profile. The mechanism by which *Brucella* saved itself without being killed in an intercellular fashion was not fully understood. However, it was reported that the main mechanism that controls intracellular replication was the oxidative explosion in host macrophages [3]. The endogenous reactive oxygen compounds of aerobic respiratory metabolism against *Brucella* strains have been shown to be exogenously produced for both endogenous and anti-*Brucella* activities of macrophages [3]. Reactive oxygen compounds responsible for oxidative stress was elevated in inflammation leading to cell damage via peroxidation of double –chain fatty, protein and DNA[17]. It was reported that this condition is responsible for the pathogenesis of diseases through accompanying the primary disease [18]. There were studies showing that oxidative stress plays a role in the pathogenesis of various bacterial infectious diseases such as Hepatitis C, Influenza, HIV, Sepsis, Crimean Congo Hemorrhagic fever, as well as non-infectious diseases [19-23]. In these cases, oxidant capacity increased and deterioration was observed in antioxidants [19]. In support of this situation, serum antioxidant activity indicators such as total peroxide malondialdehyde, paroxonase and arylesterase in osteomyelitis, tuberculosis, brusellosis and Hepatitis B infections were significantly lower than those in healthy individuals, as shown in literature [4]. Also in previous studies, reduced total antioxidant capacity in *Brucella* infection has been explained by the depletion of antioxidants as an elevated free radical scavenger [4].

Thiol groups were the main antioxidant components of serum and prevented tissue damage by reacting and neutralizing these molecules with free oxygen radicals and lipid peroxides [10]. Thiols can enter oxidation reactions, convert to the inverse forms called disulfide bonds (-S-S), which can then be converted to thiol groups. Thus thiol-disulfide homeostasis occurs [24]. In a study of thiol-disulfide balance in acute brucellosis, it was reported than an increase in disulfide could be observed without a corresponding decrease in thiol or a decrease in thiol without a corresponding increase in disulfide. In this case, when the ratio of disulfide / thiol was evaluated, it was stated that the healthiest results regarding oxidative stress can be achieved [25]. In our study, the disulphide/total thiol and disulphide /native thiol ratios were found to be statistically higher than those of healthy individuals as Kolgelier et al. [25] found in patients with acute brucellosis. As a result, increased oxidative stress can also be found in relapsed brucellosis patients.

Karaağaç et al. [26] found that after *Brucella* in-

fection treatment, oxidant capacity and antioxidant parameters reduced, and antioxidant levels increased. In this study, it has been reported that oxidant-antioxidant balance, which can be achieved by treatment with oxidative stress, may contribute to treatment outcome [26]. In our study, the high ratio of disulfide/thiol suggests that it may contribute to follow–up treatment in terms of relapse development undertreatment.

Oxidative stress-induced conformational change in the N-terminal end of albumin, metabolic ions such as cobalt and copper which tie with the N- terminal end fail due to conformational change and was called altered albumin-shaped ıschemic modified [12]. IMA was a newly developed marker that increases in ischemic and oxidative stress-related pathological conditions such as myocardial infarction, pulmonary embolism, COPD and cerebrovascular event [27]. In inflammatory diseases, high IMA levels have been shown to be indicative of oxidative stress, together with inflammation and oxidative stress associated with the pathogenesis of these diseases [28]. Furthermore, the use of IMA as a marker in infectious diseases such as sepsis and community-acquired pneumonia associated with oxidative stress and ischemic damage has been reported in the literature. In these diseases, it has been recognized as an important marker of ischemic damage in tissues and organs, helping to identify and quantify oxidative stress [13]. In our study, IMA value was statistically found to be significantly higher in patients with relapsed brucellosis than in healthy subjects. In addition, a moderately strong positive correlation was detected between disulfide/thiol ratios. This moderately strong relationship was used control the accuracy of parameters used as oxidative stress indicators in cases of relapsing brucellosis.

Limitations

Limitation in our study was firstly not compared with other oxidative stress markers used as an indicator of oxidative stress. Another limitation is that it was performed with a small number of patients.

CONCLUSION

Thiol/ disulphide balance, previously balance, previously studied in acute brucellosis, has also been shown to be oxidative in our study of relapsing Brucella cases. IMA was higher in the study group than in the control group and correlation with disulphide /thiol ratios was also considered as a sign of increased oxidative stress in relapsed brucellosis cases. Previous studies have shown that brucellosis treatment response can be followed up with oxidative stress markers and in our study; it has been shown that it can also be used as a relapse indicator.

Authors' Contribution

Study Conception: MHA, CKB, AK; Study Design: ÖK, SİY, PB; Supervision: MHA, ÖK, AK; Funding: CKB, PB, MHA; Materials: ÖK, SİY, MHA; Data Collection and/or Processing: CKB, ÖK, PB; Statistical Analysis and/or Data Interpretation: ÖK, CKB, SİY; Literature Review: AK, ÖK, CKB; Manuscript Preparation: ÖK, MHA, SİY and Critical Review: PB, AK, MHA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(1):65-73 Original Article

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Analysis of unplanned revisits and readmissions: results of the General Surgery clinic in a private hospital

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ABSTRACT

Objectives: In recent years, the rate of readmission (RA) within the first thirty days of discharge has been an important parameter for cost and quality standards. It is therefore extremely important for each center to analyze its own results and determine the factors affecting the RA rates in order to organize the measures to be taken. Another important issue, especially for centers focusing on specific areas of expertise, is unplanned revisit (RV) after discharge. Determination of these rates and reasons is of importance for every hospital and/or clinic to decrease these rates, thus increasing patient satisfaction and reducing costs. The aim of this study was to analyze RA and RV patients operated in the general surgery clinic of our hospital for a period of two years as well as factors affecting these rates.

Methods: The study included patients who were operated in the general surgery clinic of Bursa Private Medicabil Hospital between 1 January 2018 and 31 December 2019 and who revisited and were readmitted within the first thirty days of discharge. The reasons for RA/RV and time to RA/RV, and patients' treatments were investigated by comparing RA/RV patients with those who were not readmitted (NA) for demographic results at initial admission to determine the differences between these patient groups. Univariate and multivariate analyses were carried out using the SPSS software. The level of significance was set at $p < 0.05$.

Results: Of the 890 patients who were operated in our clinic throughout the study period and met the study inclusion criteria, 52 (5.8%) were included in the unplanned RA group and 107 (12%) in the unplanned RV group. The mean time to RA was 10.5 ± 7.0 days for the RV group and 8.8 ± 6.7 days for the RA group ($p = 0.17$). Thirty-two (61.5%) of the RA patients and 41 (38.3%) of the RV patients were readmitted within the first 7 days of discharge ($p = 0.003$). The multivariate analysis revealed that prolonged length of hospital stay, emergency surgery, abnormal WBC, electrolyte imbalance, and abnormal hemoglobin level were significant risk factors for RV, while the development of complications, prolonged length of hospital stay, and advanced age were significant risk factors for RA.

Conclusions: This study analyzing the RA and RV patients operated in the general surgery clinic of a private hospital demonstrated that the most important reasons for RA were nonspecific and preventable. Patients who developed complications, had prolonged length of hospital stay, and were at an advanced age had a higher rate of RA, while patients who had prolonged length of hospital stay, underwent emergency surgery, and had biochemical problems at initial admission had a higher rate of RV. Focusing on these patients during and after discharge and increasing home care facilities can solve the problems of many patients without admitting them to the hospital. This will be a factor that would improve patient satisfaction while reducing costs.

Keywords: Unplanned readmission, unplanned revisit, predictive factors, surgery

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In 2009, the post-discharge 30-day readmission (RA) rates for selected diseases were reported by the Centers for Medicare and Medicaid Services (CMS) in the United States (US) [1]. Since a significant portion of readmissions is preventable and costly, financial penalties have been initiated for hospitals with an above-average RA rate in the USA as of 2012. Hospitals were first penalized for readmissions of patients with acute myocardial infarction, heart failure, and pneumonia, and patients with chronic obstructive pulmonary disease and knee-hip arthroplasty were then included in this approach. This program is planned to be expanded to include all surgical procedures in the near future [2, 3]. Reducing these rates with in-hospital and external organizations based on the determined risk factors has become an important target for the centers. Today, these rates are also considered an important parameter reflecting the quality of care of hospitals [4].

Classical RA is defined as readmission to any center for any reason within the first thirty days after a primary disease or surgery. This rate can be affected by many parameters, including the biology of the disease, patient's condition, surgical factors, social factors, patient care, and the healthcare system. The infrastructure of each center, patient and disease groups have differences [5, 6]. It is therefore extremely important for each center to analyze its own results and determine the factors affecting the RA rates in order to organize the measures to be taken. Another important issue, especially for centers focusing on specific areas of expertise, is unplanned revisit (RV) after discharge. Many patients present both to emergency departments and outpatient clinics with various complaints other than their routine follow-ups and undergo various diagnostic and therapeutic interventions. Although this is not considered as important as RA, it appears to be an important issue when considered from the point of patient satisfaction, labor loss, and the stress it creates on the patient and physician. The issue of RV has been a subject of interest for ambulatory surgery clinics, especially plastic surgery and ear-nose-throat clinics [7, 8]. In this respect, there was only one study investigating RA and RV following short-stay thyroidectomy [9]. There is no study on RV including all surgical cases. Moreover, there was no Turkey-based study on unplanned RA.

The aim of this study was to analyze patients with unplanned RA and unplanned RV to the general surgery clinic of our hospital within the first 30 days of discharge for a period of 2 years as well as factors affecting these rates.

METHODS

Study Groups and Demographic Data

Patients operated in the General Surgery Clinic of Bursa Private Medicabil Hospital between 2018 and 2019 were retrospectively analyzed. Our hospital has been accredited twice by JCI and has a bed capacity of 100 and level 3 intensive care facilities. The approval for the study was obtained from the hospital ethics committee (Ethics committee approval date and number: 01.04.2019/11113). The study included patients who only spent the night after surgery (index surgery) in the hospital. Day-case procedures and endoscopic procedures were excluded. Furthermore, patients who died at the hospital after the first operation, patients who were included in the routine chemotherapy program in this period and admitted for this reason, and those whose RA reason could not be fully determined and file data could not be accessed for data analysis were not included in the study.

The patients were divided into three groups: 1) No admitted (NA): Those who were not admitted within the first 30 days of discharge after surgery, except for their routine follow-ups. 2) Revisited (RV): Patients who underwent surgery and revisited the emergency department or an outpatient clinic with any complaints other than their routine follow-up appointment within the first 30 days of discharge but were not hospitalized. 3) Readmission (RA) group included patients who underwent surgery, readmitted to the hospital with any complaints other than their routine follow-up appointment within the first 30 days of discharge, and were treated as an inpatient due to this admission.

The distribution of the patients between the two groups is shown in Fig. 1. The patients' demographic data, American Society of Anesthesiologists (ASA) scores, comorbidities, emergency-elective surgery, wound condition, fluid-electrolyte imbalance, hemoglobin level, abnormal White Blood Cell (WBC) level (< 4000 or > 11.000 per microliter) at initial admission, presence of malnutrition, anatomical location of surgery (gastrointestinal surgery, breast-thyroid sur-

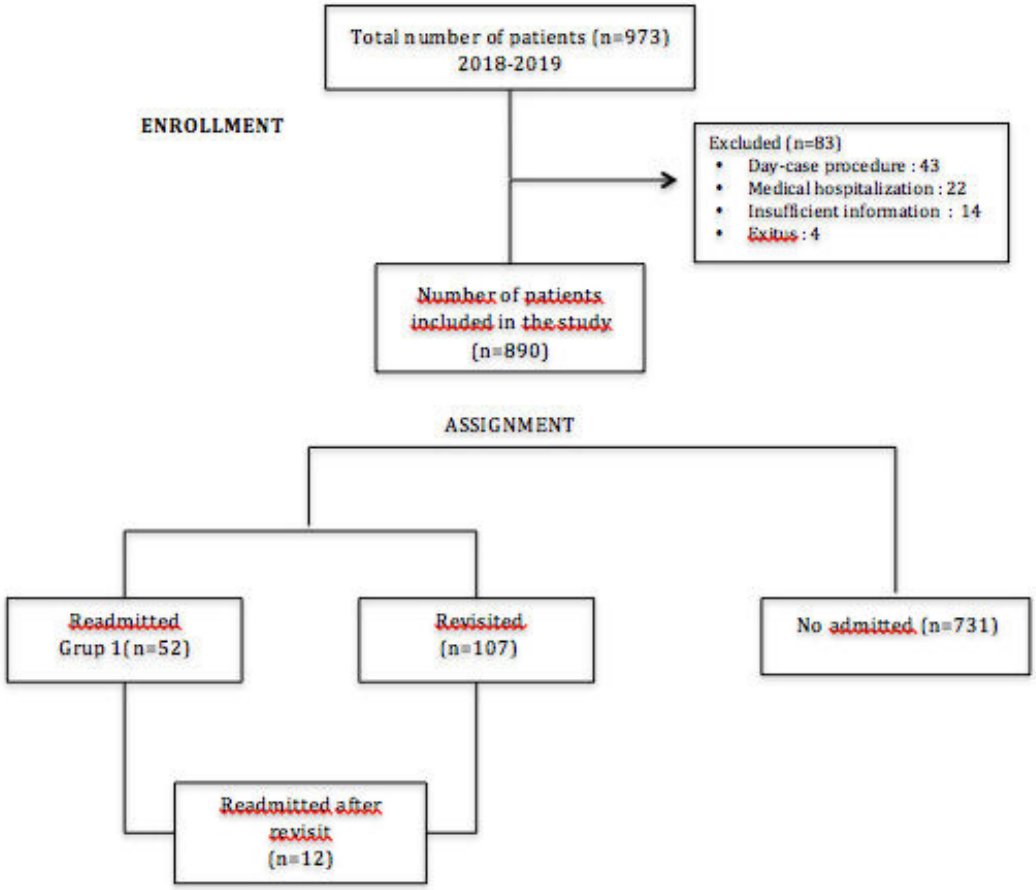

Fig. 1. Analysis of patients and distribution of study groups.

gery, extra-abdominal surgery), laparoscopic surgery, length of hospital stay, complications developed during the first operation, time to readmission and reasons for readmission were recorded. A complication was defined as any morbidity that developed intraoperatively and postoperatively during the hospitalization period, and the Clavien-Dindo classification was used to rank a complication [10]. The definition of malnutrition was made based on the NRS-2002 assessment [11]. Patients with a score of 3 points and above in this assessment were included in this group. The presence of electrolyte imbalance was considered an abnormality in any electrolyte level in the routine biochemistry evaluation prior to the first surgery. Patients with normal values and not requiring biochemical analysis were included in the group without electrolyte imbalance. A low hemoglobin level was defined as a concentration below 10 g/dL. The Centers for Disease Control and Prevention (CDC) surgical wound classification system was used for wound classification, and the cases were grouped as clean, clean/contaminated, contaminated, and dirty [12]. Reasons for readmission and interventions performed at readmission were recorded. The records were reviewed by the coordinating nurse of the study (NS). Patients who revisited and were readmitted within the first thirty days of discharge (RV or RA) were identified from the hospital electronic system. These patients were reevaluated by the team that performed the surgery (HO, MN, EC) and were grouped by reevaluating whether they had planned or unplanned readmission within the scope of the routine appointment schedule. Patients with incomplete information in their records were reached by phone.

Statistical Analysis

The patient groups were compared by univariate and multivariate analyses for the analyzed factors. The SPSS version 2.0 software was used for the statistical analysis. Categorical values were presented as percentage frequency, while quantitative values were given as arithmetic mean ± standard deviation. Pear-

son's chi-squared test and the t-test were used for the univariate analysis. The level of statistical significance level was set at $p < 0.05$ bidirectionally. Factors with significant or nearly significant values in the univariate analysis were included in the multivariate logistic regression analysis to determine independent factors. Before including quantitative values in the multivariate analysis, cut-off values were calculated by ROC analysis and converted into categorical values. In the RV group, these values were calculated as a cut-off value of 50.5 (Area Under the Curve [AUC]: 0.565, 95% CI: 0.51-0.61, $p = 0.01$) for age and 9 days (AUC: 0.68, 95% CI: 0.63-0.73, $p < 0.001$) for the length of stay. In the readmission group, the same values were determined as a cut-off value of 51.5 (AUC: 0.706, 95% CI: 0.624-0.787, $p < 0.001$) for age and 10.5 days (AUC: 0.639, 95% CI: 0.54-0.73, $p = 0.004$) for the length of stay.

RESULTS

Demographic Results

Of the 890 patients who were operated in our clinic throughout the study period and met the study inclusion criteria, 52 (5.8%) were included in the RA group and 107 (12%) in the RV group. The main reasons for readmission were gastrointestinal complaints

Table 1. Reasons of revisited and readmitted patients for admission and diagnostic/therapeutic interventions performed

Revisited (n = 107)		Readmitted (n = 52)	
Reasons, n (%)		**Reasons, n (%)**	
Gastrointestinal problems (Nausea, vomiting, dehydration)	23 (21.5%)	Gastrointestinal problems (Nausea, vomiting, dehydration)	14 (26.9%)
Wound complications (Seroma, wound infections)	26 (24.3%)	Wound complications (deep wound infections)	11 (21.1%)
Pain (wound, abdominal)	27 (25.3%)	Organ space infection	9 (17%)
Nonspecific symptoms	9 (8.4%)	Ileus	9 (17%)
Cardiac	7 (6.5%)	Nutrition	5 (9.6%)
Pulmonary	7 (6.5%)	Pain (wound, abdominal)	4 (7.6%)
Urinary tract infection	3 (2.8%	Bleeding	4 (7.6%)
Neurological	2 (1.3%)	Missed pathology	2 (3.8%)
Hypothyroidism	2 (1.3%)	Cardiac	1 (1.9%)
Fever (catheter-related)	1 (0.9%	Pulmonary	1 (1.9%)
		Neurological	1 (1.9%)
Interventions performed*, n (%)		**Interventions performed, n (%)**	
Short-term observation	52 (48.5%)	Medical treatment (Intravenous fluid-drug-antibiotic therapy-analgesia-nutrition)	22(42.3%)
Radiological diagnostic procedure	38 (35.5%)	Secondary surgery	13(25%)
Prescription or recommendation only	33 (30.8%)	Wound care	11(21.1%)
Wound care	27 (25.2%)	Percutaneous or endoscopic intervention	6 (11.5%)
Consultation	21 (19.6%)		

*Some patients underwent more than one intervention

Table 2. Univariate analysis results of the comparison of demographics and operative characteristics associated with readmission

Factor	No admitted (n = 731)	Revisited (n = 107)	Readmitted (n = 52)	*p* value
Age (years)[α]	47.3 ± 16.7	51.4±17.2	59.6 ±15.1	**0.005**[*]
	(18-89.45)	(18-88.50)	(28-88.60)	**< 0.001**[&]
				< 0.001[ϕ]
Length of stay (days)[α]	1.68 ± 1.7	3.97 ± 4.71	5.7 ± 6.4	**0.005**[*]
	(1-21.1)	(1-20.1)	(1-30.3)	**0.000**[&]
				0.001[ϕ]
Comorbidity	81 (11%)	18 (17.6%)	11 (21%)	0.089[*]
				0.024[&]
				0.47[ϕ]
Time to readmission (days)	-	10.5 ± 7.0	8.8 ± 6.7	0.17
		(1-30.10)	(1-29.7)	
Wound				
Clean	268 (36.6%)	13 (12.1%)	10 (19.2%)	**< 0.001**[*]
Clean/contam.	269 (36.7%)	32 (30%)	9 (17.3%)	**< 0.001**[&]
Contaminated	124 (16.9%)	41 (38.3%)	28 (53.9%)	0.068[ϕ]
Dirty	70 (9.5%)	20 (18.7%)	5 (9.6%)	
ASA score				0.06[*]
1-2	704 (96%)	99 (92.5%)	40 (77%)	**< 0.001**[&]
3-4	27 (4%)	8 (7.5%)	12 (23%)	**0.005**[ϕ]
Malnutrition	23 (3.1%)	11 (10.2%)	12 (23%)	**< 0.001**[*]
				< 0.001[&]
				0.031[ϕ]
Abnormal Hemoglobin	21 (2.8%)	12 (11.2%)	13 (25%)	**< 0.001**[*]
				< 0.001[&]
				0.015[ϕ]
Electrolyte imbalance	35 (4.7%)	20 (18.7%)	5 (9.6%)	**< 0.001**[*]
				0.13[&]
				0.129[ϕ]
Abnormal WBC	94 (12.8%)	24 (22.4%)	25 (48%)	**0.007**[*]
				< 0.001[&]
				0.001[ϕ]
Emergency surgery	62 (8.4%)	24 (22.4%)	19 (36.5%)	**< 0.001**[*]
				< 0.001[&]
				0.06[ϕ]
Type of surgery				
GIS	412 (56.4%)	115 (72.3%)	40 (77%)	**0.0003**[*]
Extra-abdominal Perianal	215 (29.4%)	24 (15.1%)	8 (15.3%)	**0.014**[&]
	104 (14.2%)	20 (12.6%)	4 (7.7%)	0.62[ϕ]
Laparoscopic surgery	317 (43.3%)	48 (44.8%)	9 (17%)	0.77[*]
				0.0002[&]
				0.0006[ϕ]
Complication (+)	31 (4.2%)	4 (3.9%)	17 (32.6%)	
1	17	1	2	0.82[*]
2	12	2	7	**0.001**[&]
3	2	1	6	**0.001**[ϕ]
4	-	-	2	

α = values in parenthesis are given as median and range, ***** = revisited vs. no admitted, **&** =readmitted vs. no admitted, **ϕ** = revisited vs. readmitted, WBC = White Blood Cell Count, contam = Contaminated, GIS = Gastrointestinal Surgery

(RV:21.5% vs. RA: 26.9%) and wound problems (RV:24.3% vs. RA:26.9%) in both groups. The pain was a significant factor in the RV group (25.3%). Twelve (11.2%) patients in the RV group were admitted to the hospital for the second time and hospitalized. The reasons for readmission and interventions performed in both groups are shown in Table 1. Three of the patients in the RA group (5.7%, 3/52) died after their second hospitalization. One of these patients was operated for sepsis after an anastomotic leak, one patient for cardiac problem, and the other was urgently operated for strangulated hernia and died due to developing decompensated cirrhosis after discharge.

Results of Univariate and Multivariate Analyses

The results of the univariate analysis are shown in Table 2. It was found that the RA group patients were older, had a longer length of hospital stay, and had more systemic problems than both the NA and RV patients. Electrolyte imbalance was a more common reason for readmission in the RV group. The rates of RV and RA were higher in patients who underwent gastrointestinal surgery, but there was no difference between these two groups. While the rate of RA was lower in patients who underwent laparoscopic surgery, it was higher in those who developed complications.

Table 3. Independent risk factors associated with unplanned revisit for patients undergoing surgery

Factors	OR	95% CI	*p* value
Longer length of stay > 9 day	2.2	1.61-3.02	**< 0.001**
Emergency surgery	1.44	1.22-1.69	**< 0.001**
Abnormal WBC	1.36	1.20-1.54	**0.009**
Presence of electrolyte imbalance	1.19	1.12-1.25	**0.001**
Abnormal hemoglobin level	1.84	1.34-2.52	**0.001**

Table 4. Independent risk factors associated with unplanned readmission for patients undergoing surgery

Factors	OR	95% CI	*p* value
Complication (+)	12.04	3.79-38.1	<0.001
Longer length of stay (> 11 day)	6.67	2.01-22.1	0.013
Advanced age (> 51.5 years)	3.1	1.54-6.21	0.01

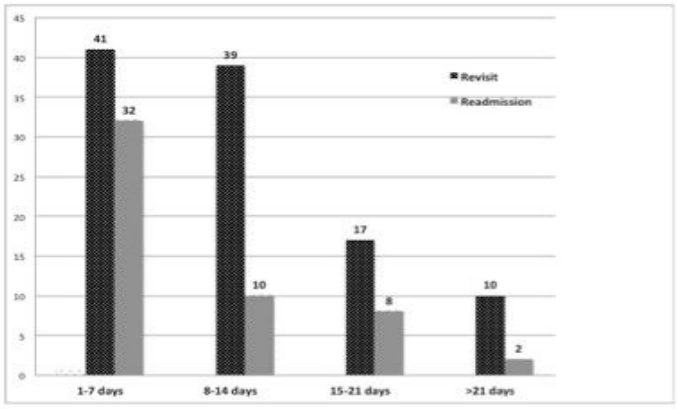

Fig. 2. Correlation between time and revisited and readmitted patients. Forty-one (38%) of the revisited patients and 32 (61.5%) of the readmitted patients were readmitted within the first week of discharge. This difference was statistically significant (chi-square: 8.88, $p = 0.030$).

The multivariate analysis revealed that prolonged length of stay, emergency surgery, abnormal WBC, electrolyte imbalance, and abnormal hemoglobin level were significant risk factors for RV, while the development of a complication, prolonged length of stay, and advanced age were significant risk factors for RA (Tables 3 and 4).

Time to Readmission

The mean time to readmission was 10.5 ± 7.0 days for the RV group and 8.8 ± 6.7 days for the RA group ($p = 0.17$). Although the mean time to readmission was not statistically significant, 32 (61.5%) of the RA patients and 41 (38.3%) of the RV patients were readmitted within the first 7 days of discharge ($p = 0.003$). The readmission times are presented on the basis of weekly periods in Fig. 2.

DISCUSSION

Statement of Principal Findings

This study analyzing and comparing two years of unplanned RV and RA patients operated in the general surgery clinic of a private hospital demonstrated a 30-day RV rate of 12% and a 30-day RA rate of 5.8%. The main reasons for readmission were gastrointestinal complaints (RV: 21.5% vs. RA: 26.9%) and wound problems (RV: 24.3% vs. RA: 26.9%) in both groups. The pain was a significant factor in the RV group (25.3%). The multivariate analysis showed that the

RV-related factors were prolonged length of stay, emergency surgery, abnormal WBC, electrolyte imbalance, and abnormal hemoglobin level, while the development of a complication, prolonged length of stay, and advanced age were significant factors for RA.

Interpretation within the Context of the Wider Literature

The concept of RA is a well-defined measure of quality and is widely used in many countries. Studies have found the most important reasons for postoperative RA as wound complications, gastrointestinal problems, postoperative pain, activation of associated illness, substance abuse, and socioeconomic status [13]. A study conducted in France found the rate of readmission for all gastrointestinal surgery cases as 11.3%. The most important reasons for readmission were gastrointestinal complications (27%), surgical site infection (22%), digestive problems (10%), and medical problems (41%). The presence of cancer or dyspnea, complexity of the surgery, and respiratory complications were found to be the most important risk factors [14]. Two studies conducted in the UK at an interval of about 10 years found this rate as 6.8% and 4.7% and reported the most important reasons for readmission as surgical infections (57%) and postoperative pain (29%) [15]. A study from China found the rate of readmission after colorectal surgery as 18.6% and reported the presence of preoperative comorbidity as the most important risk factor [16, 17]. Our RA rate is lower than the results reported in the USA and is similar to the results reported by studies of European origin. However, such comparisons may not be very reliable. Because the infrastructure of each clinic and its patient group operated do not have the same risk factors. For this reason, it will be of more significance for each clinic to carry out its own risk analysis. In the analysis of the reasons for readmission, gastrointestinal problems ranked first, while the surgical factors ranked second among our patients.

One of the important points is to understand the main factors for RA and to reduce preventable admissions with the improvements to be made based on these factors. It is very difficult to establish a standard model due to the problem's multifactorial nature, conditions specific to each clinic, and differences in their patient groups. Many studies have shown a significant relationship between the length of hospital stay at initial hospitalization and readmission. In general, the patient's physiological capacity, the complexity of the surgery, and the development of complications are predictive of prolonged length of stay [18]. Our study demonstrated that the development of complications in index surgery, prolonged length of hospital stay, and advanced age were the most important risk factors for readmission. Especially the patients who developed complications had a 12-fold higher RA rate than those who did not develop complications. Complications develop depending on many factors (patient, disease, surgeon, surgical intervention). Therefore, it may be possible to reduce the complication rate by analyzing each case in itself. Since gastrointestinal problems are the most important reason for RA, post-discharge close follow-up of patients with these risk factors, keeping the lines of communication open, providing good training at discharge and providing home care services, if necessary, are extremely important to reduce preventable readmissions.

Although the RA rates and reasons, and measures to be taken have been analyzed in a broad sense, the reasons for unplanned RV are not a well-studied subject after general surgical procedures. The subject of RV has mostly been analyzed after a day-case otological surgery, sinonasal surgery, and facial surgery. These studies have reported an RV rate ranging between 2.3-5.2% [19-21]. Another study found the RV rate after thyroidectomy as 3.6%. The multivariate analysis revealed that a high ASA score and renal failure were the most important factors affecting this rate. The most important reasons for RV were cough/sputum discharge and wound-related problems [9]. This rate was found to be 12% in our study. The therapeutic and diagnostic procedures performed on most patients, time spent in the hospital, negative effects on the work schedule, and dissatisfaction constitute an important problem. Moreover, it significantly increases costs, though not as much as RA. Considering the reasons of our patients for RV, it seems that the problems can be resolved without visiting the hospital in a significant number of patients. Only 12 (11.2%) of these patients were readmitted after the initial RV and were hospitalized. Pain complaints, simple GIS symptoms, and non-surgical systemic problems were determined as the most important reasons in this group. It seems that patients who underwent laparoscopic surgery had a lower rate of RA and a higher rate of RV. Today,

when a significantly higher number of minimally invasive procedures and day-case surgeries have been performed, it is suggested that the RV problem is an important issue after general surgical interventions, which should also be studied.

Implications for Policy, Practice and Research

The prevention of complications during index surgeries will decrease the rates of RA and RV. However, this rate is relatively stable for surgical patients. For this reason, identifying patients who may develop complications in advance and making the necessary improvements will help decrease the rate of RA/RV. The study by Merkow *et al*. [22] showed that only 2.3% of readmissions were associated with exacerbation or recurrence of pre-existing complications. Studies have shown that at least half of readmissions can be prevented with better follow-up and care, and 41.8% of patients have the potential to be treated outside the hospital [23]. It seems possible to solve a significant proportion of readmissions by expanding non-hospital approaches. Some changes have been made in our hospital and clinic to reduce the rates of unplanned and preventable RA and RV. Patients with risk factors are called at certain periods after discharge. Furthermore, the opportunity to consult a physician is facilitated by using the internet and social media. Home care service is provided to patients in this risk group and those who demand. The effectiveness of this system will be evaluated by future studies.

Strengths and Limitations

The major limitation of our study was its retrospective design and including the results of a single clinic. Moreover, non-hospital, healthcare-related factors, and social factors were not analyzed. Furthermore, patients who were readmitted to other hospitals were attempted to be analyzed by phone calls, but it was not possible to reach their records. However, this study aimed to analyze the results of a single surgical clinic and may therefore demonstrate some measures to be taken to reduce readmissions more clearly. It will be relatively easier to prospectively evaluate the improvements to be made with the results obtained from this study. Another limitation is that the study included a relatively small number of patient groups. However, large and multi-center studies may have a small effect on centers' own practices, considering in terms of quality control study and measures to be taken. Therefore, local results are of importance in this respect. Due to the retrospective nature of our study, some of the unplanned RV events in the outpatient clinic may have been missed or the planned RV patients may have been evaluated as unplanned RV. However, this possibility was attempted to be reduced by measures such as analyzing only the patients of a single team that operated these patients as well as re-analyzing suspicious conditions.

CONCLUSION

In conclusion, this study analyzed the RA and RV patients who were operated in a general surgery clinic. Preventable or non-preventable factors associated with readmission and revisit were analyzed. Patients who developed complications, had prolonged length of hospital stay, and were at an advanced age had a higher rate of RA, while patients who had prolonged length of hospital stay, underwent emergency surgery, and had biochemical problems at initial admission had a higher rate of RV. It was found that these rates were affected by the current physical condition of the patient rather than the operation itself. The results of this study, which reflect the results of a single team, can be useful for many centers in the same category. Focusing on these patients during and after discharge and improving out-of-hospital care facilities with a multidisciplinary approach can reduce the rates of unplanned RA and RV.

Authors' Contribution

Study Conception: MN, HÖ, EÇ, NS; Study Design: MN, HÖ, EÇ; Supervision: HÖ; Funding: MN, HÖ; Materials: NS; Data Collection and/or Processing: MN, HÖ, EÇ, NS; Statistical Analysis and/or Data Interpretation: MN, HÖ, EÇ, NS; Literature Review: MN, HÖ, EÇ, NS; Manuscript Preparation: MN, HÖ, EÇ and Critical Review: HÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any

grant during conduction or writing of this study.

Statement of data availability

Our data was sought from the hospital records system. The data that support the results of this study can be obtained from the corresponding author upon reasonable request.

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The European Research Journal 2022;8(1):74-83 Original Article

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The difference between gender in terms of nomophobia in Turkey: a meta-analysis

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ABSTRACT

Objectives: Technology unfortunately even though making our life easier, causes a lot of psychological problems when it is not used reasonably. One of them is the inability to live without a smartphone: nomophobia. This meta-analysis study considered nomophobia in Turkey in terms of gender.

Methods: Using "nomophobia", "Nomophobia Scale ", "Nomophobia Questionnaire (NMP-Q)", "NMP-Q"and "smartphone" keywords, 9 electronic bibliographic databases from the internet were searched for studies related to the nomophobia scale. The inclusion criteria were determined as studies that the nomophobia questionnaire (NMP-Q) utilized to Turkish people, published in English or Turkish, and reported the questionnaire score by mean/standard deviation according to gender. The mean age and sample size ratio, which were thought to have an effect on heterogeneity, are analyzed by meta-regression.

Results: From the 9 electronic bibliographic databases, a total of 3370 studies were located, and only 10 meetings the inclusion criteria. It revealed that females are found to be more nomofobic than males according to Nomophobia Questionnaire (NMP-Q). The mean age and sample size ratio, which were thought to have an effect on heterogeneity, are analyzed by meta-regression.

Conclusions: The gender difference was found to be statistically non-significant in 2 of the 10 studies included in the meta-analysis. By enlarging the sample size, which is one of the advantages of meta-analysis, the difference between gender is determined more accurately.

Keywords: Nomophobia questionnaire, NMP-Q, meta-analysis, gender, smartphone

With the latest developments, mobile phones are no longer used only for communication with another person via verbal communication or text message, but also provide versatile communication possibilities with smartphone features. Smartphones have become attractive to millions of people because of advanced capacity, constantly updated operating systems, and outperforming mobile phones in terms of processing power [1]. According to the "TURKSTAT Household Information Technology Usage Survey (2004-2018)", the rate of having mobile phones/smartphones in households is increased from 53.7 percent to 98.7 between 2004 to 2018. While the use of mobile phones and smartphones facilitates our lives in all areas, some negative effects such as addiction or anxiety occur.

Nomophobia, which is called the new phobia of the modern age, comes from the English word nomophobia "NO MObile PHOBIA". In psychology, it is defined as the irrational fear experienced by an individual when he / she cannot access or communicate on their mobile device [2, 3].

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In nomophobia, the individual begins to feel anxious when he forgets to take his phone with him, when his phone is out of charge or out of range. This anxiety negatively affects the concentration of the individual on daily work in his life [4].

In order to determine the nomophobia level Nomophobia Questionnaire (NMP-Q) is developed by Yıldırım and Correira [3]. The Turkish version is formatted by Yıldırım *et al*. [5]. It contains a 7-point Likert type, 20 items, and four subdimensions. The validity and reliability of the scale were assessed and referred to it. Four subdimensions are named as follows; unable to access information (1-4 items), giving up convenience (5-9 items), unable to communicate (10-15 items), and losing connectedness (16-20 items). By summing up each item response score, the nomophobia scale scoring is ranged between 20 and 140. According to mild, moderate, and severe nomophobia levels, the scoring is ranged 21-59, 60-99, and 100-140, respectively [3].

After Yıldırım *et al*. [5] transform the Nomophobia Questionnaire (NMP-Q) to the Turkish version, the application of the transformed questionnaire in Turkey has increased. Numerous studies have been independently conducted across Turkey to reveal nomophobia. Yıldırım *et al*. [5] showed that the rate of the nomophobic behavior of university students is 42.6%. Onal and Onal [6] aimed to determine high school students' use of smartphones and their nomophobia levels, for this purpose 767 students participated in the research. The results showed that high school students were nomophobic at a moderate level [6]. Adnan and Gezgin [7] utilized the transformed scale on 433 university students found the level of nomophobia is over average. Hosgor and Hosgor [8] conducted on the university students in Istanbul who studying on Department of Health Management, they revealed also over average nomophobic behavior. Güllüce *et al*. [9] searched the relationship between subjective well-being and nomophobia levels of Ardahan University students. They determined that men are less nomophobic than women [9]. Gezgin and Cakir [10] analyzed the prevalence of nomophobia among high school students according to smartphone usage, gender, class levels, mother's and mother's education level, smartphone usage time, and mobile internet usage. Yavuz *et al*. [11] examined nomophobia on an adolescent population related to alexithymia and metacognitive problems. Arslan *et al*. [12] conducted research on teachers to find out the correlation of nomophobia and fear of missing out. Akhoroz [13] examined the correlation between the nomophobia and personality traits among preservice teachers. Arpaci *et al*. [14] related the nomophobia to attachment for college students and concluded the gender factor is important in mindfulness-based treatments. Çelik İnce [15] searched the correlation between self-esteem and obesity and nomophobia. The analysis results demonstrated moderate nomophobia and non-significant correlation [15].

In parallel with the increase in the generality of smartphone using, nomophobia, and the related scientific studies number are also increasing. Hence, it is appropriate to use meta-analysis, which is a statistical method combining and interpreting the results of more than one scientific study. This meta-analysis examined all studies published between January 2016 and December 2020.

The main purpose of this study is to determine whether nomophobia differs according to gender by meta-analysis. On the other hand, to assess the effects of the mean age of each study and sample size ratio on the difference mean, meta-regression is applied. The analyzes are made using the "meta" and "metafor" packages in the R package.

METHODS

In recent years meta-analysis has gained importance with the ease of access to scientific studies on any subject. Meta-analysis is a statistical analysis method that allows combining the results obtained from many studies on a specific subject and independent from each other [16]. Since meta-analysis is considered as the combination of the studies, it is important to determine all publications related to the subject.

Meta-analysis can be applied in combining experimental studies rather than theoretical studies. The meta-analysis method differs according to the reported summary statistics.

The benefits of the meta-analysis are expressed as follows: by increasing the sample size making a decision about the uncertainty and estimating the effect size in case of conflict of independent study results [17].

Effect size is the basic unit of meta-analysis and represents the direction and size of the relationship of interest. By standardizing the results of the studies, it provides the opportunity to directly compare. Mean difference, correlation coefficient and odds ratio are examples of different types of effect sizes [16, 18]. The calculation of effect size differs according to study purpose, design and data type. If the data type nominal, continuous or indicate a relationship respectively the proportions, mean, and the correlation coefficient are used [19]. It is possible to convert effect sizes to each other by using transformation formulas [16].

Fixed and random effect models are the two main models used in meta-analysis. The characteristic structure of the study and the source of error are important in model selection. When studies are obtained from published literature, it is more appropriate to use the random effect model [16].

One of the graphics that provides a better understanding of the results visually in meta-analysis is the forest graph. This graph shows the effect size of each study, 95% or 99% confidence intervals, weights, and combined effect size. This graph provides information about the variability among the estimates of each study [20].

Mean and variance (or standard deviation) are the main descriptive statistics in the meta-analysis of continuous data. Usually, to compare the means of two independent groups the raw mean or the standardized mean difference are preferred effect sizes. The raw (Unstandardized) mean difference is given in Eq. (1) which is used when all studies in the analysis use the same scale (for example blood pressure). Standardized mean differences (d) and (g) are given in Eq. (2) and Eq. (7) used when the different studies use different instruments (such as different psychological or educational tests) to assess the outcome. Since the scale of measurement will differ from study to study so it will not meaningful to combine raw mean difference.

The raw (Unstandardized) mean difference and standardized mean difference for sample estimate are given as;

$$D = \bar{X}_1 - \bar{X}_2 \quad (1)$$

$$d = \frac{\bar{X}_1 - \bar{X}_2}{S_{within}} \quad (2)$$

The variance of D and d are given as;

$$V_D = \frac{S_1^2}{n_1} + \frac{S_2^2}{n_2} \quad (3)$$

$$S_{within} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}} \quad (4)$$

$$V_d = \frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2)} \quad (5)$$

where $\bar{X}_1, \bar{X}_2$, S_1^2 *and* S_2^2 be the sample mean and variance of the two groups, and n_1 and n_2 be the sample size in the two groups. In small samples, a correction factor is used to remove a slight bias of d that called Hedges'g. $\bar{X}_1$

Differences in study design (scale, population, etc.) lead to heterogeneity. Therefore, heterogeneity analysis is important in the meta-analysis, and heterogeneity between studies can be tested with various statistical tests. The heterogeneity concern the true variance, not sampling error. Commonly used measurements in decomposing true variance; Q is the statistic (squared of weighted deviations) and the ratio of the true heterogeneity in the total observed variance (I^2). The I^2 statistic takes values between 0% and 100%, regardless of the effect size type (mean, ratio or correlation) used in the meta-analysis, values at 25%, 50% and 75% are considered low, medium and high heterogeneity, respectively.

$$J = 1 - \frac{3}{4sd - 1} \quad (6)$$

$$g = J \times d \quad (7)$$

$$V_g = J^2 \times V_d \quad (8)$$

In revealing the causes of heterogeneity on the basis of moderator variable (covariate or covariant); subgroup analysis is used for the categorical moderator variable, and multiple meta-regression analysis is used for the continuous moderator variable [16]. In this study, briefly mentioned on meta-regression.

Meta-regression

In general, regression is defined as a model that determines the relationship between a dependent variable and an independent variable (s). For given n observations the model for regression is given as;

Where y_i (i = 1,2,…,n) is a observed values, β k×1 coefficients vector, x_i is a 1×k vector of covariate.

$$y_i = x_i'\beta + \varepsilon_i \qquad \varepsilon_i \sim N(0, \sigma_i^2) \tag{9}$$

While classic regression based on individual observations, the meta-regression based on study-level summary data.

For given n study fixed-effects meta-regression is given in Eq (10),

Even though fixed-effects assume zero heterogeneity, it used mostly in replicated experiment applications [16].

$$\begin{aligned} &y_i = x_i'\beta + \varepsilon_i \qquad y_i \sim N(\theta_i, \sigma_i^2), \\ &\theta_i \sim N(\theta + x_i'\beta, \sigma_a^2) \qquad \varepsilon_i \sim N(0, \sigma_i^2) \end{aligned} \tag{10}$$

For given n study random-effects meta-regression is given in Eq (11),

$$\begin{aligned} &y_i = x_i'\beta + u_i + \varepsilon_i \qquad y_i \sim N(\theta_i, \sigma_a^2 + \sigma_i^2), \\ &\theta_i \sim N(\theta + x_i'\beta, \sigma_a^2), \\ &u_i \sim N(0, \tau^2), \\ &\varepsilon_i \sim N(0, \sigma_i^2) \end{aligned} \tag{11}$$

Where y_i (i = 1, 2, n) is an observed values, β k × 1 coe fficients vector, x_i is a 1 × k vector of covariate values in study i [21].

The significance of the regression coefficient (H_0:β_i=0) can be evaluated with the Z test;

$$Z = \frac{\hat{\beta}_j}{Se_{\hat{\beta}_j}} \tag{12}$$

where $\hat{\beta}_j$ is the least square estimator of the parameter and the $Se_{\hat{\beta}_j}$ is the estimated standard error of $\hat{\beta}_j$. under H_0 Eq. (12) has the standard normal distribution.

A bubble plot is a useful tool that plotting the effect size versus a continuous covariate. The fitted line with the circle demonstrates the estimates from each study, and the circle size differing with the weighted of studies.

RESULTS

This study search whether nomophobia, which is the phobia of the inability to live without a smartphone, that occurs with the widespread use of smartphones, differs according to gender. Using "nomophobia", "Nomophobia Scale", "Nomophobia Questionnaire (NMP-Q)", "NMP-Q"and "smartphone" keywords, 9 electronic bibliographic databases searched the studies related to the nomophobia scale. The inclusion criteria were studies that the nomophobia questionnaire (NMP-Q) utilized to Turkish people, published in English or Turkish, and report the questionnaire score by mean/standard deviation according to gender. A total of 3370 studies were located, with 10 meeting the inclusion criteria (Fig. 1).

Some of the studies are reported as a mean of Likert scale scores and others as a total score. To uniform, these reported studies, by multiplying 20 (number of items in the scale) to mean of Likert scale scores the total score is obtained [3].

Based on gender difference the information of included 10 studies in the meta-analysis is given in Table 1.

In order to determine the difference between gender according to the mean nomophobia scale score, a meta-analysis conducted using standard mean difference effect size (SMD). The results summarized in Table 2.

It can be seen from Table 2 that the mean nomophobia scale score for both the fixed and random effect model varies according to gender ($p < 0.05$). For both models, the mean score of females was found to be higher than males. Also, heterogeneity is statistically significant ($p < 0.05$). The cause of heterogeneity might be due to utilizing different population characteristics (age, city, etc.).

Since the included studies in the meta-analysis are compiled from published literature the use of the random-effect model is considered more appropriate. Therefore, the forest plot only shows the random-effect model results.

The Forest plot divided into eleven columns (Fig. 2). The results of each study results are displayed in rows. The first column ("study") lists the identification of each study included in the meta-analysis. The second and fifth columns represents the total number of participants of each study. The third and sixth columns displays the male and female mean values of NMP-Q scale of each study. The fourth and seventh columns displays the male and female standard deviation values of NMP-Q scale of each study. The eighth column rep-

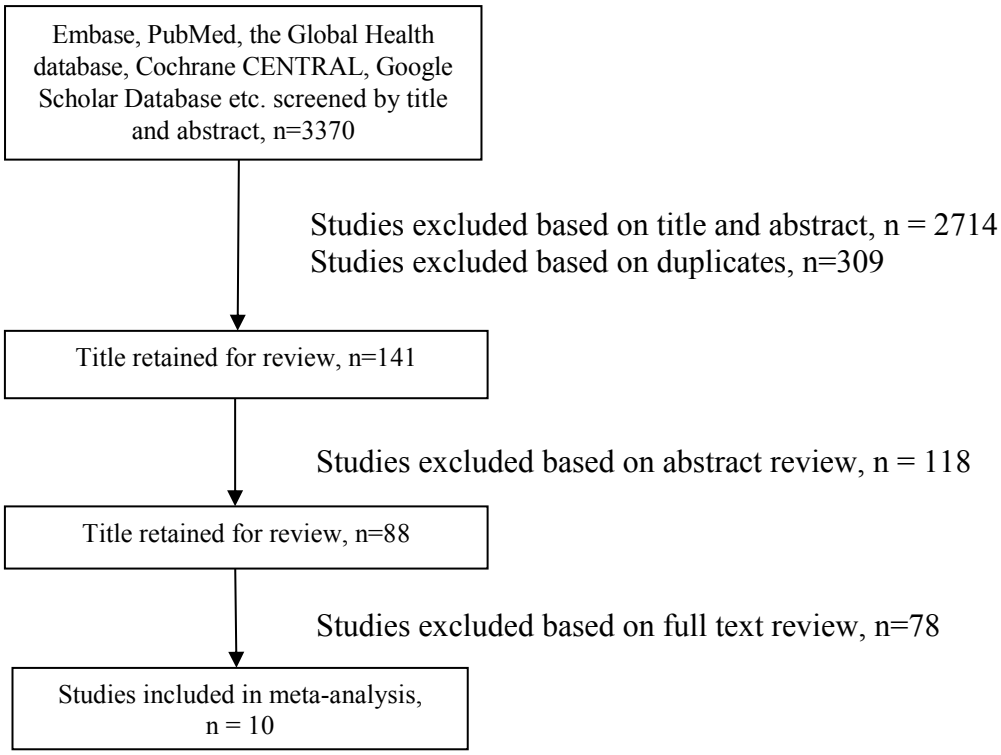

Fig. 1. Summary of literature search and selection of studies.

resents the standardized mean difference (effect estimates) of each study included in the meta-analysis and related confidence interval. The effect estimate of each study depicted with a box situated in line. The size of the box is directly related to the reciprocal of the variance (weighting) of each study in the meta-analysis. The length of the confidence interval (CI) represented with the horizontal line (Whiskers) through the box. In the case of the long lines, the confidence interval gets wider and this means that the less precise the study results. The ninth column represents the effect estimates of each study numerically. The tenth column represents the confidence interval of each study numerically. The last column depicts the weight (in %) indicates the weighting or influence of each study on the overall results of the meta-analysis of all included studies.

In the last row of the graph, the diamond illustrates

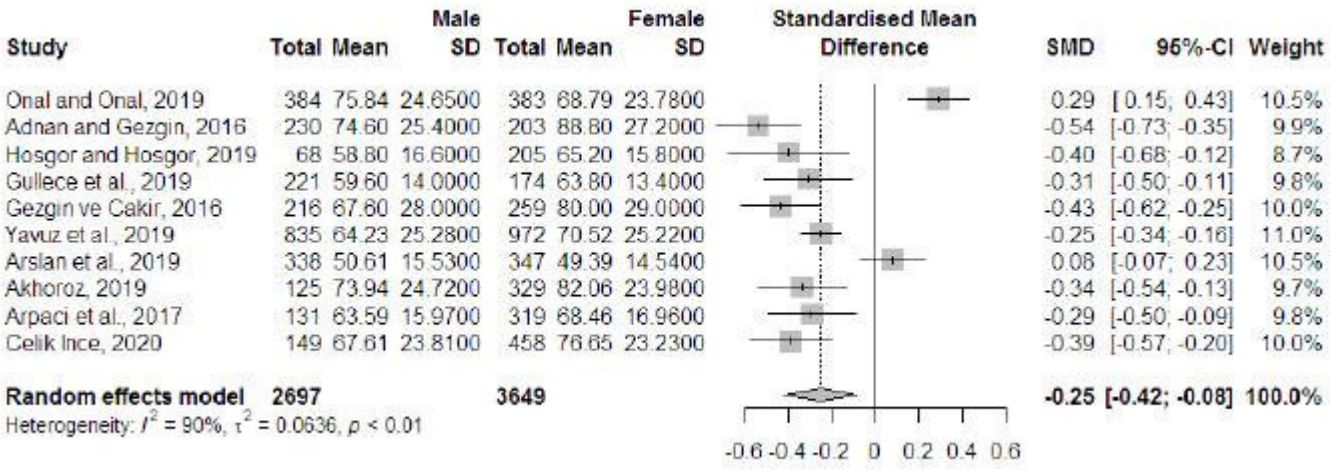

Fig. 2. Forest plot of standardized mean difference.

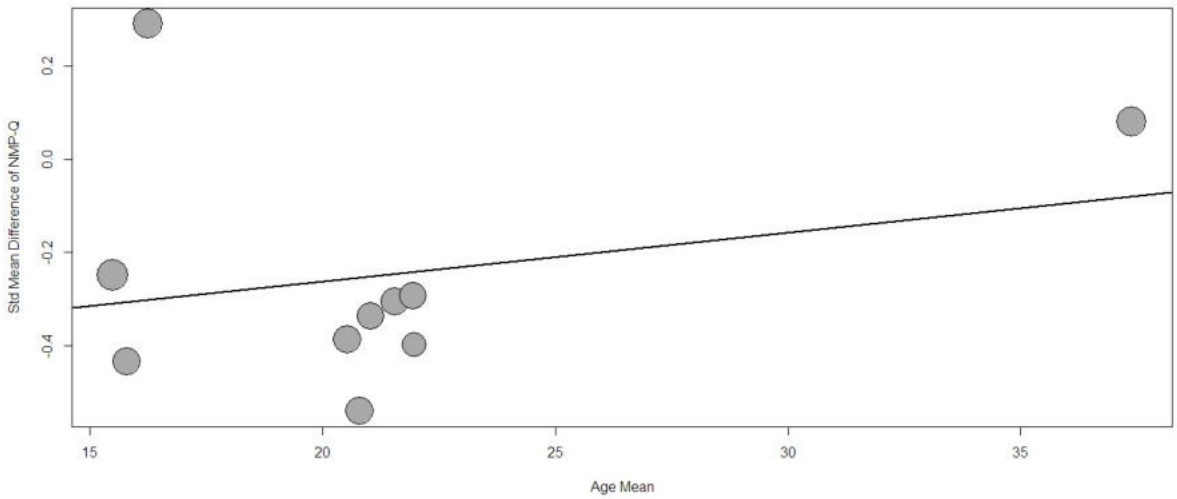

Fig. 3. **Bubble plot of age mean.**

the overall result of the meta-analysis. The width of the diamond indicates the width of the overall confidence interval. The most reliable test for heterogeneity is given at the bottom of the graph on the left hand (I^2). Checking the overlap of the confidence interval is a useful visual guide to assessing heterogeneity. If the confidence interval of all studies overlaps than studies are regarded as homogeneous.

The Forest plot shows that, the standardized mean difference for gender ranging between 0.08 and -0.54. Eight out of ten studies received negative values and the overall standardized mean difference is -0.25. This shows that females have a higher mean nomophobia score than males. The confidence intervals of studies are narrow so the results of the studies are precision. On the other hand, whether the confidence intervals contain zero or not makes it easy to determine whether there is a statistical difference between the groups. While only one out of ten studies showed no difference in mean nomophobia score for females and males [12], this difference appears to be significant for the overall effect. The weighting of each study included in the meta-analysis changed between 8 and 11. The study with the smallest variance influenced the most to the overall effect result [11]). This can be seen from the box and the horizontal line (Whiskers) through the box. Yavuz *et al.*'s study [11] give relatively the biggest box and narrowest line. The heterogeneity can

Table 1. **Information of included studies in the meta-analysis**

Study	Male		Female		Mean Age	Ratio of Sample Size of Males to Females
	Sample size	Mean ± SD	Sample size	Mean ± SD		
Onal and Onal, 2019 [6]	384	75.84 ± 24.65	383	68.79 ± 23.78	16.25	1.00
Adnan and Gezgin, 2016 [7]	230	74.6 ± 25.4	203	88.8 ± 27.2	20.79	1.13
Hosgor and Hosgor, 2019 [8]	68	58.8 ± 16.6	205	65.2 ± 15.8	21.97	0.33
Güllüce *et al.*, 2019 [9]	221	59.6 ± 14	174	63.8 ± 13.4	21.55	1.27
Gezgin and Cakir, 2016 [10]	216	67.6 ± 28	259	80 ± 29	15.8	0.83
Yavuz *et al.*, 2019 [11]	835	64.23 ± 25.28	972	70.52 ± 25.22	15.5	0.86
Arslan *et al.*, 2019 [12]	338	50.61 ± 15.53	347	49.39 ± 14.54	37.38	0.97
Akhoroz, 2019 [13]	125	73.94 ± 24.72	329	82.06 ± 23.98	21.02	0.38
Arpaci *et al.*, 2017 [14]	131	63.59 ± 15.97	319	68.46 ± 16.96	21.94	0.41
Çelik İnce, 2021 [15]	149	67.61 ± 23.81	458	76.65 ± 23.23	20.53	0.33

SD = standard deviation

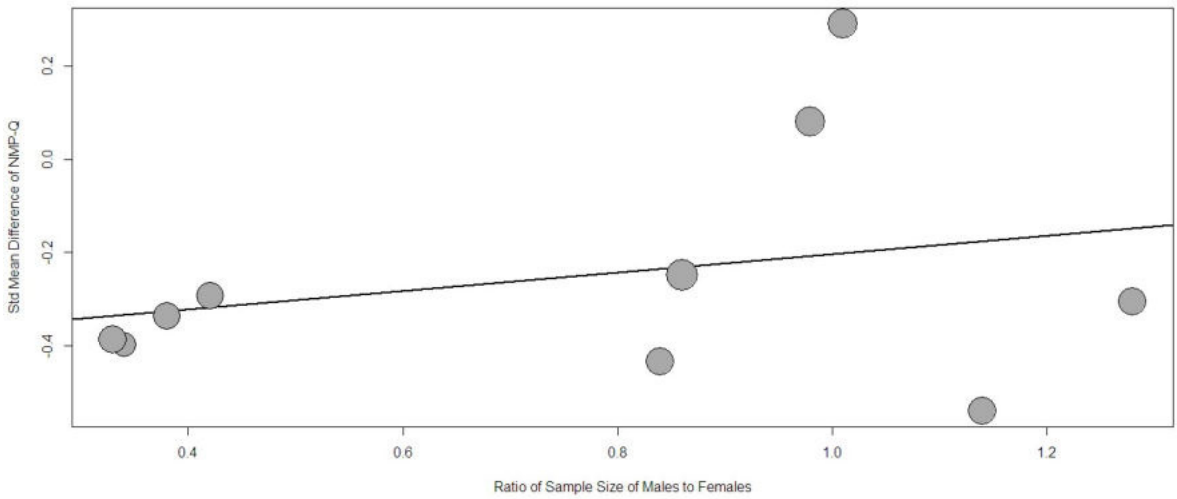

Fig. 4. Bubble plot of ratio of sample size.

be observed by the not overlapping confidence interval of all studies (Fig. 2).

Finally, the overall standardized mean difference -0.25 (95% CI, -0.42 to -0.08), there is a statistically significant difference between females and males, meaning that the mean nomophobia score is higher in the females compared to the males. Also indicated significant between-study heterogeneity (Q = 87.66, $p < 0.05$) with $I^2 = 90\%$, which means that 90% of observed variance comes from real differences between studies and, as such, can potentially be explained by study-level covariates.

Although the literature is searched for the same scale, it is examined by meta-regression whether the age difference of the population to which the scale is utilized is effective in heterogeneity. The mean age ranged between 15.5 and 37.38 (Table 1).

Table 3 shows that the regression coefficients are not statistically significant ($p > 0.05$). Therefore, it is concluded that the mean age covariate does not affect the mean nomophobia scale score in terms of gender. This conclusion can also be reached according to whether the 95% confidence interval of each coefficient includes zero or not. The 95% confidence interval of both coefficients contains zero.

The linear model obtained by meta-regression is graphically displayed with a bubble graph. It is given in Fig. 3 for age mean. The circles in the graph are proportional to the weight of each study. The ten studies considered seem to have almost the same weight. The middle line shows the estimated values of each study. Although it is not statistically significant, it appears from the graph that there is difference in terms of mean nomophobia scale score between males and females as the age increases. In terms of gender, the mean nomophobia scale score difference is mostly in favor of males between the ages of 15-20, this difference changing in favor of females the ages of 21-25,

Table 2. Results of meta-analysis

Model	SMD	95% CI	z	*p* value	Test of heterogeneity
Fixed effect	-0.20	[-0.25-0.15]	-7.76	0.0001*	Q = 87.88 (*p* value = 0.0001)
Random effects	-0.25	[-0.42-0.08]	-2.93	0.0034*	

Table 3. Results of meta-regression analysis for age mean

	Coefficient estimate	Coefficient SE	z	*p* value	95% CI
Intercept	-0.47	0.33	-1.43	0.15	[-1.12-0.17]
Age mean	0.01	0.01	0.70	0.48	[-0.02-0.04]

Table 4. Results of meta-regression analysis for the ratio of sample size

	Coefficient estimate	Coefficient SE	z	*p* value	95% CI
Intercept	-0.40	0.21	-1.91	0.06	[-0.81-0.01]
Ratio of sample size	0.20	0.25	0.79	0.43	[-0.29-0.69]

for over 35 ages this difference again changes in favor of males; the score of males increases more than females.

In four of the ten studies included in the meta-analysis, the sample sizes of males and females are different. To determine whether this difference is important for heterogeneity, the ratio of a males sample size to a females sample size is examined by meta-regression. The ratio is ranged between 0.33 and 1.28 (Table 1).

Table 4 indicates that the regression coefficients are not statistically significant ($p > 0.05$). Therefore, it is concluded that the ratio of sample size covariate does not affect the mean nomophobia scale score in terms of gender. This conclusion can also be reached according to whether the 95% confidence interval of each coefficient includes zero or not. The 95% confidence interval of both coefficients contains zero.

Ones again the linear model obtained by meta-regression is graphically displayed with a bubble graph. It is given in Fig. 4 for the ratio of sample size.

The circles in the graph are proportional to the weight of each study. The ten studies considered seem to have almost the same weight. The middle line shows the estimated values of each study. Although not statistically significant, interesting results are obtained from the bubble graph. It can be seen from the graph that females have higher than males mean nomophobia scale scores in case of the ratio of sample size is smaller or greater than 1. However, when this ratio is 1 or very close to 1 the mean score of males is higher than females (Fig. 4).

DISCUSSION

In the age of information, the features of smartphones are increasing day by day depending on the need. Especially with the pandemic we have been experiencing since 2020, phones are not only communication and messaging tools, but meeting, education, banking, food ordering, food shopping, socializing, etc. every need is at our fingertips. Unfortunately, a device that meets such needs becomes indispensable.

In this study, the difference between gender was investigated based on the Nomophobia Questionnaire (NMP-Q). Adnan and Gezgin [7] utilized the transformed scale on 433 university students' nomophobia was observed to make no difference for gender. The difference between gender was statistically significant for 273 students who were studying at the Department of Health Management [8]. Again, the difference by gender was found to be statistically significant in the scale applied on 395 university students [9]. A similar result was obtained for 450 university students [14]. In the case of the study conducted on 607 nursing students, the difference between gender was significant also [15].

When the study group consisted of 475 high school students, the difference was statistically significant for gender [10]. Also, when the study was conducted on 1817 participants (n = 972, 54% female, n = 835, 46% male) the difference between gender was statistically significant [11]. For 765 adolescents participants, the difference was statistically significant for gender [6].

To examine teachers' nomophobia, data were collected from a total of 685 teachers, no difference was observed between gender [12]. But for preservice teachers, the difference was statistically significant [13].

Except for the teachers' study group, the nomophobia scores of females were higher than males were observed. The gender difference was found statistically non-significant in 2 of 10 studies included in the meta-analysis.

CONCLUSION

It is no longer just for calling and messaging, but for banking, entertainment, etc. smartphones, which are also used for, have become a part of our lives. Un-

fortunately, misusing this technological convenience leads to addiction in some people. The inability to live without a smartphone is called nomophobia (NO MOBile PHOBIA) in psychology. The Nomophobia Questionnaire (NMP–Q) has been developed to measure the level of nomophobia.

With the increasing scientific studies on this subject, the necessity to combine and interpret these studies statistically is revealed. In this study, the difference in mean nomophobia scale score according to gender is discussed by meta-analysis. 10 studies are included in the analysis according to the inclusion criteria. As a result of the analysis, it is determined that females had higher mean nomophobia scale scores than males.

The mean age and sample size ratio, which were thought to have an effect on heterogeneity, are analyzed by meta-regression. Although the effect of the two covariates considered is not statistically significant in heterogeneity, females between the ages of 20-25 have higher mean scores than males, while this situation reverses at the other ages. An interesting result is obtained for the sample size ratio. When the ratio is 1 or very close to 1, males have a higher mean score than females, while the ratio is less or more than 1, the mean score of females has increased than males. This result may be totally coincidental. For making more accurate inferences, more studies must be utilized.

Most of the studies discussed in this study were applied to student groups. Applying nomophobia studies to different sample groups is important in determining the difference between gender in the population.

Authors' Contribution

Study Conception: EA; Study Design: EA; Supervision: EA; Funding: EA; Materials: EA; Data Collection and/or Processing: EA; Statistical Analysis and/or Data Interpretation: EA; Literature Review: EA; Manuscript Preparation: EA and Critical Review: EA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Is tocilizumab effective in cytokine release syndrome in patients diagnosed with COVID-19?: a retrospective preliminary study

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ABSTRACT

Objectives: Although the prognosis is good in the vast majority of patients who are diagnosed with COVID-19, there are cases in which Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure occur rapidly and result in death in a short time. It has been reported that severe clinical presentation is caused by cytokine release syndrome, and studies are currently conducted on treatments to reduce mortality in these patients. There are studies reporting the positive effects of anti-Human IL-6 Receptor Monoclonal Antibody, tocilizumab (TCZ), which specifically inhibits the functions of IL-6, in cases with cytokine storm. Data on TCZ use in intensive care are very limited.

Methods: The medical records of 20 patients diagnosed with COVID-19 who were treated with standard treatment and TCZ in the ICU were retrospectively reviewed.

Results: Twenty patients were included in the review. Nine (45%) received TCZ. The median length of stay in the ICU was 20 days in the TCZ group, and 14 days in the standard treatment group ($p = 0.21$). Mortality rate was 22.2% in TCZ group and 45.5% in the standard treatment group ($p = 0.27$).

Conclusions: At day 28, mortality rate and clinical improvement was not statistically different in patients receiving standard treatment with TCZ and patients in standard treatment group. Additional data are needed to understand the eficacy and safety of TCZ.

Keywords: COVID-19, cytokine release syndrome, tocilizumab

Coronaviruses are RNA viruses that can infect humans and many animal species [1]. Although they cause seasonal respiratory tract infections in humans, new Coronavirus species, especially the ones that have been seen since 2002, have led to clinical presentations characterized by a more severe respiratory tract infection. These are Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) infections that emerged in 2003 and 2012 respectively and caused hundreds of deaths [1, 2]. On December 31, 2019, cases of pneumonia of unknown etiology were reported in Wuhan, China's Hubei province, and a new coronavirus (2019-nCoV) that was not previously detected in humans was identified as a causative agent. Later, the name of the 2019-nCoV disease was accepted as coronavirus disease 2019 (COVID-19), and it spread rapidly in China and many other countries, reaching the pandemic level [3].

Although the prognosis is generally good in COVID-19, it has been reported that approximately 20% of the patients develop severe pneumonia that can progress to Acute Respiratory Distress Syndrome (ARDS) [1]. Clinical data show that in patients with ARDS, the virus can induce an exaggerated abnormal

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host immune response characterized by an excessive increase of pro-inflammatory cytokines similar to the clinical and serological features of cytokine release syndrome [4]. Cytokine release syndrome is one of the main causes of the clinical picture resulting in cardiovascular collapse, multiple organ failure and rapid death. Therefore, in cases which cytokine storm develops, it is thought that neutralization of inflammatory factors is an effective treatment in reducing mortality [5].

The main driver of cytokine storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. Although positive clinical results have been reported in patients who developed cytokine release syndrome and used anti-human IL-6 receptor monoclonal antibody tocilizumab (TCZ), which specifically inhibits the functions of IL-6, data with high level of evidence about the effect of TCZ on inflammatory activity patients with COVID-19 is not yet available [6, 7].

There is currently no standardized therapeutic scheme for the use and dosage of tocilizumab in the treatment of cytokine storm caused by COVID-19, and data on its use in intensive care are very limited. In our retrospective study, we aimed to reveal the effects of using TCZ on clinical results and laboratory values in patients diagnosed with COVID-19 and developed cytokine release syndrome in the intensive care unit (ICU).

METHODS

Study Design and Participants

Patients above 18 years of age who were admitted to Bursa City Hospital, Department of Anesthesiology and Reanimation Intensive Care Unit between April 5 – June 20, 2020 and diagnosed COVID-19 which was confirmed with reverse transcription polymerase chain reaction (rRT-PCR) and received either a standard treatment with TCZ and standard treatment without TCZ were enrolled in the study. Patients who received immune plasma and steroid treatment were excluded. The study was approved by the ethical committee of Uludag University Faculty of Medicine.

Procedures

The data of the patients were obtained from the medical records. The demographic data (age, gender), various scores for predicting morbidity and mortality (Acute Physiology and Chronic Health Evaluation [APACHE] II and Sequential Organ Failure Assessment [SOFA]), body temperature, PaO2/FiO2 ratio and duration of ICU hospitalization were recorded for each patient. The latest C-reactive protein (CRP), IL-6, ferritin, lactate dehydrogenase (LDH), d-dimer, lymphocyte and neutrophil values before TCZ administration were chosen as pre-treatment values and changes in values within the seven-day period after TCZ administration were taken into account. In the standard treatment group, the values of these data at the time of ICU hospitalization were recorded. The demographic characteristics, ICU hospitalization scores, laboratory data, length of ICU hospitalization and 28-day mortality rates of the patient group treated with tocilizumab and standard therapy were compared. In addition, the pre-treatment laboratory and clinical data of the TCZ group were compared with the data on the 3rd and 7th days of treatment.

Treatment

In our intensive care unit, this treatment was applied in cases diagnosed with pneumonia, in line with the recommendations of the Ministry of Health General Directorate of Public Health Covid-19 (SARS-CoV-2) Guide [8]: Hydroxychloroquine with a loading dose of 400 mg twice daily followed by 200 mg per day twice daily for additional five days, favipravir with a loading dose of 1600mg twice daily followed by 600 mg per day twice daily for additional five days and azithromycin with a loading dose of 500 mg daily followed by 250 mg per day for additional five days, unless contraindicated. CRP, IL-6, ferritin, neutrophil, lymphocyte count, procalcitonin (PCT) and D-dimer values were monitored daily or at 48 hour intervals according to the fever and PaO2/FiO2 ratio of the cases. In patients with suspected cytokine release syndrome in their follow-up, after secondary bacterial infection was excluded, the first dose of TCZ was administered as a 1-hour infusion of 400 mg, and the second dose of 400 mg was administered 24 hours later to those who did not show improvement in PaO2/FiO2 ratio.

Adverse Effects

The occurrence of adverse events was recorded daily and focused on: bacterial or fungal infections,

elevation aspartat transaminase (AST) or alanine aminotransaminase (ALT) level > 5 fold the upper limit of normal range (AST:0-40 IU/L, ALT:0-41 IU/L), neutropenia < 1.0 103/µL, thrombocytopenia < 100 103/µL).

Statistical Analysis

The data were analyzed using SPSS 26.0 for Windows (SPSS, Chicago, IL). The frequency and descriptive statistics were calculated. The descriptive statistics were presented as ± SD for continuous variables, while they were presented as median (min-max) for the categorical variables. Independent samples t test (Student's t test) and Mann Whitney-U test were performed to compare variables between two treatment groups. Before performing these tests, the data were explored by using Kolmogorov-Smirnov test which datas were normally distributed. Chi-Square test was used to compare categorical variables between the groups. Friedman test was used to compare the varibles of patients whom treatment (72th. hour and 1st. week). To find out which pairs are different, pairwise comparions post-hoc Bonferroni test was carried out. The level of statistical significance was set at $p < 0.05$.

RESULTS

During the study, a total of 31 patients whose COVID-19 diagnosis was confirmed by rRT-PCR were followed up in the intensive care unit. Nine (29%) cases received TCZ with standard therapy, and 11 cases only received standard therapy. Three patients given immune plasma, 7 patients treated with steroids and 1 patient for whom sufficient data could not be obtained were excluded from the study. Baseline characteristics of both groups are summarized in Table 1. Median age was similar in the tocilizumab and the standard treatment group: 62 (46-76), compared to 65

Table 1. Baseline characteristics of the patients

	Tocilizumab (n = 9)	Standartd treatmant (n = 11)	*p* value
Age (years) (median, min-max)	62.67 (46-79)	65 (37-81)	0.673
Gender (n, % of total)			
Male	9 (45%)	7 (35%)	0.094
Female	0 (0%)	4 (20%)	
Body mass index (kg/m^2) (median, min-max)	26.97 (25-30)	28.45 (23-33)	0.254
APACHE-II (median, min-max)	19.11 (7-30)	17.72 (7-31)	0.666
SOFA (median, min-max)	4 (3-11)	4 (3-14)	0.261
Fever (ºC) (median, min-max)	37.5 (36.8-39.1)	37.5 (36.5-39.3)	0.987
Co-morbidites (n, % of total)			
Diabtes mellitus	2 (10%)	3 (15%)	0.604
Hypertension	3 (15%)	4 (20%)	0.630
COPD	0 (0%)	1 (5%)	0.550
Coronary artery disease	3 (15%)	0 (0%)	0.074
Cerebrovascular disease	2 (10%)	0 (0%)	0.189
Patients required invasive mechanical ventilation (n, % of total)	4 (20%)	4 (20%)	0.535
Patients required high flow oxygen therapy (n, % of total)	5 (25%)	7 (35%)	0.535

APACHE II = Acute Physiology and Choronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, COPD = Choronic obstructive pulmonary disaese

Table 2. Laboratory features of COVID-19 patients treated with tocilizumab compared with patients with standard treatment

	Tocilizumab (n = 9)	Standartd treatmant (n = 11)	Reference range	*p* value
Interleukin-6 level (pg/mL)	153.650 ± 3 (39-283)	296 ± 143 (15-1655)	0-7	0.930
C-reactive protein (mg/L)	159.5 ± 78.9 (47.5-287)	126.5 ± 62.1 (51-248)	0-5	0.307
Procalcitonin (µg/L)	1.0±0.2 (0.12-2.15)	1.1 ± 0.4 (0.06-5.27)	-	0.824
Ferritin (ng/mL)	1494.2 ± 438.5 (963-2000)	992.3 ± 676.1 (185-2000)	30-400	0.071
Neutrophil count (10^3/µL)	9.9 ± 3.0 (5.7-13.9)	7.0 ± 2.4 (3.7-11.3)	1.8-6.98	**0.028***
Lymphocyte count (10^3/µL)	0.85 ± 0.12 (0.34-1.70)	0.87 ± 0.14 (0.48-2.17)	1.26-3.35	.882
Platelet count (10^3/µL)	304.8 ± 93.8 (155-467)	255.4 ± 96.3 (109-422)	166-308	0.264
Lactate dehydrogenase (IU/L)	499.1 ± 170.7 (277-789)	467.2 ± 146.0 (246-743)	135-225	0.658
D-dimer (ug/FEU/ml)	3.2 ± 3.1 (0.65-8.93)	2.5 ± 3.4 (0.25-9.87)	0-0.5	0.665
Troponin (ng/L)	31.6 ± 44.4 (7.7-111)	26.1 ± 31.9 (5-111)	-	0.781

*The level of statistical significance was set at $p < 0.05$, ** Data were presented as mean ± SD (min-max)

(37-81) years respectively ($p = 0.67$). Median body mass index was 26 and 28 in the tocilizumab and the standard treatment group, respectively ($p = 0.25$). In addition, no statistically significant difference was found between the two groups in terms of ICU hospitalization scores and co-morbidities.

The median values of PaO2/FiO2 ratios were 79.7 and 107.2 in the TCZ and standard treatment groups, respectively ($p = 0.60$). When we evaluated the two groups within themselves, the PaO_2/FiO_2 ratios in the first week were 159.2 ± 70.2 ($p = 0.001$) and 125.6 ± 63.6 ($p = 0.006$), respectively, and the increase in both groups was statistically significant.

While 4 (44.4%) patients were under invasive mechanical ventilation (IMV) support before treatment in the TCZ group, 5 (55.6%) patients received high flow oxygen therapy (HFOT). While the need for IMV support continued in 4 patients in the first week after the treatment, one of the patients who received HFOT was taken to nasal oxygen support. In the standard treatment group, 4 (36.5%) patients were under IMV support, while 7 (63.6%) patients were undergoing HFOT, and the patients' IMV and HFOT need continued on the 7th day of their admission to the ICU.

There was no statistically significant difference between the laboratory findings of both groups, except for neutrophil levels (Table 2). The length of stay in the ICU was 20.63 ± 12.58 days in the tocilizumab group and 14.36 ± 8.78 dayin the standard treatment group ($p = 0.21$). By day 28, two (22.2%) patients in the tocilizumab group compared to 5 (%45,5) patients in the standard treatment group died ($p = 0.27$). The time from onset of symptoms to treatment administration in the TCZ group was 11.5 ± 5.7 (5-19) days.

Before starting TCZ therapy, CRP (159.5 mg/L), ferritin (1494.2 ng/mL), IL-6 (153.6 pg/mL) values

were significantly higher in all patients. A statistically significant decrease was found in CRP (14 mg/L) and ferritin (897.1 ng/mL) values in the first week after treatment (p = 0.001 and p = 0.018, respectively). There was a significant rapid increase (1958 pg/mL) in IL-6 values on the 3rd day after treatment and a decreasing trend was observed. The SOFA scores, PaO2/FiO2 ratios and laboratory findings of the patients in TCZ group at pre-treatment, at the 72nd hour and at the first week of treatment are summarized in Table 3. While CRP values improved rapidly after TCZ treatment, there was a gradual decrease in ferritin values.

Thrombocytopenia, neutropenia, and elevation of liver enzymes were not detected in the TCZ group during ICU hospitalization. Ventilator-associated pneumonia developed in one patient (11.1%) in this group, and central catheter-related bloodstream infection developed in one patient (9.1%) in the standard treatment group.

All patients had chest computed tomography at the time of their admission to ICU and all had bilateral lung diseases. In TCZ group, 5 patients had bilateral ground glass opacities with peripheral and central distribution, 3 patients had bilateral ground glass opacities with peripheral distribution and bilateral lower lobes were involved in only one patient. In standart treatment group, 2 patients had bilateral ground glass opacities with peripheral and central distribution, 5 patients had bilateral ground glass opacities with peripheral distribution and bilateral lower lobes were involved in 4 patients.

DISCUSSION

Although the mechanism of organ dysfunctions in severe COVID-19 cases is not clearly demonstrated, it has been revealed that at least some of the organ dysfunctions are immune-mediated with the increase in proinflammatory cytokine levels such as tumor necrosis factor -α, IL-1β, IL-6, which play a role in cytokine storm. As a result of these studies, in addition to antiviral and supportive treatments, immunotherapeutic agents were used in severe COVID-19 infection [9-11].

In this study, in which we share preliminary data regarding TCZ use in patients diagnosed with COVID-19 in Bursa City Hospital, in the province of Bursa where the number of cases are one of the highest in Turkey; we found that the use of tocilizumab did not significantly affect the 28-day ICU stay compared

Table 3. Parameters at admission, 72 hours and 1 week after treatment with tocilizumab

	Before treatment	72 hours after treatment	1 week after treatment	*p* value	Pairwise comparisons		
					Before treatment vs at 72 hours	72 hours after vs at 1st week	Before treatment vs after 1st week
SOFA (respiratory)	4 (0-4)	3 (0-4)	2.5 (0-4)	0.007*	0.634	0.634	0.037*
PaO2/FiO2 Ratio	79.7 ± 15.9 (59-105)	117.7 ± 38.5 (78-202)	159.2 ± 70.2 (83-296)	0.001*	0.073	0.401	0.001*
Interleukin-6 level (pg/mL)	153.650 ± 3 (39-283)	1938 ± 2049.1	1588.8 ± 1522.4 (223-3504)	0.015*	0.004*	0.343	0.058
C-reactive protein (mg/L)	159.5 ± 78.9 (47.5-287)	61 ± 77.3	14 ± 8.6 (3.1-26)	0.001*	0.061	0.061	0.001*
Ferritin (ng/mL)	1494.2 ± 438.5	1101.3 ± 497.8 (594-2000)	897.1 ± 343.3 (649-1716)	0.021*	0.952	0.240	0.018*
Neutrophil count (103/µL)	9.94 ± 3.07 (5.77-13.9)	7.67 ± 5.11 (2.16-15.7)	8.65 ± 7.11 (3.6-23.6)	0.417	-	-	-

SOFA = Sequential Organ Failure Assessment, *The level of statistical significance was set at p<0.05, **Data were presented as mean ± SD (min-max)

to standard treatment.

TCZ treatment was applied in our clinic in line with the recommendations of the Ministry of Health Guide: For the diagnosis of macrophage activation syndrome (MAS) characterized by cytokine storm, changes in clinical and laboratory findings within hours or days should be considered instead of cross-sectional evaluation based on one measurement [8]. In our study, the average time from the onset of symptoms of COVID-19 infection to administration of TCZ was 11 days. Radbel *et al*. [12] applied TCZ treatment on the 9th day after the onset of symptoms in one patient and on the 7th day in one patient, and they reported poor results in both cases. In a study using tocilizumab on average 2 days after the onset of symptoms, shorter invasive mechanical ventilation and clinical recovery time were reported, although not statistically significant [13]. These studies demonstrate the need for clinical research to determine optimal patient selection and timing.

There are no data with a high level of evidence regarding the dose of TCZ use [12, 14, 15]. Considering the changes in clinical and laboratory findings, TCZ in our clinic was administered as a second dose of 400 mg within 24 hours. Despite the usage of high dose TCZ, thrombocytopenia, neutropenia and increase in liver enzymes were not observed.

In our study, all patients had bilateral lung disease and we compared the two groups. Results of the comparison demonstrate that there was no difference in not only the baseline characteristics of the two groups but also we found no significant difference in terms of intensive care stay and PaO2/FiO2 ratios betwee two groups.

As a result of the analysis of pre-treatment laboratory data in the TCZ group, we found that CRP and ferritin decreased consistently when compared with the values on the 3rd and 7th days of treatment. Whether this downward trend of acute phase reactants is related to clinical improvement is not yet clear [13]. The dramatic CRP reduction after treatment is a pharmacological effect of TCZ through the IL-6 receptor. We found a significant increase in IL-6 levels on the 3rd day of treatment. A possible explanation for this is that tocilizumab inhibits receptor-mediated clearance of IL-6, leading to serum accumulation [14].

Limitations

The lack of a control group and the small number of patients in studies with promising results regarding tocilizumab are important limitations of these studies [9, 14, 16]. In studies conducted after these studies and comparing tocilizumab with standard therapy, no statistical difference was found between the groups in mortality and intensive care unit admission [17, 18].

CONCLUSION

The diagnosis of MAS and initiation of treatment within hours is very important in suppressing the cytokine storm. Although it is still difficult to use laboratory parameters to define the disease activity, the amount of dose to be applied in the treatment is not clear. We think that the results of clinical studies with large patient groups will provide further evidence on the role of IL-6 blockade in severe COVID-19 patients and whether tocilizumab treatment is safe and effective.

Authors' Contribution

Study Conception: GÇ, ST, AS; Study Design: GÇ, ST, AS; Supervision: GÇ, ST, NBS; Funding: GÇ; Materials: GÇ; Data Collection and/or Processing: ST, AS, NBS; Statistical Analysis and/or Data Interpretation: GÇ, ST, AS, NBS; Literature Review: GÇ, AS, NBS; Manuscript Preparation GÇ, ST and Critical Review: GÇ, ST, AS, NBS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of anesthetic approaches to surgical patients during early COVID-19 pandemic

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ABSTRACT

Objectives: We aimed to evaluate the anesthetic approaches of patients who underwent surgery in our hospital during the early COVID-19 pandemic period.

Methods: All patients admitted to general surgery (GS), orthopedics, neurosurgery (NS), urology, cardiovascular surgery (CVS), thoracic surgery, ear nose throat, and plastic and reconstructive surgery at the operating rooms in our hospital in early pandemic periods were scanned retrospectively. Demographical data, surgical indications, urgency, anesthetic methods, and complications are evaluated. Anesthetic methods used in the operations were examined as general anesthesia, regional anesthesia, and sedoanalgesia. In addition, patients' hospital stay period, intensive care unit admission rate, 30 days mortality, and COVID-19 positivity after surgery were examined.

Results: Two hundred and ninety patients were admitted for operation in our hospital during a pandemic. CVS, Orthopedics, and GS were departments that admitted the most number of patients with ratios of 27.2%, 26.2%, and 25.2% respectively. The patients who underwent emergency surgery were seen in the CVS with 79 patients and the orthopedics with 73 patients. In anesthesia management, the application rate of general anesthesia was 44.1%, regional anesthesia 33.1%, and sedoanalgesia 22.8%. Totally 61 patients were admitted to ICU. According to surgical branches, 30-day mortality rates were determined as 8.3% in NS, 6.6% in GS, 3.8% in CVS, and 2.7% in orthopedics respectively. 4 patients were postoperative COVID-19 positive in total.

Conclusions: Anesthetic approaches in surgical patients may affect the length of hospital stay, referral to the intensive care unit, and mortality in the early period of the COVID-19 pandemic.

Keywords: COVID-19, pandemics, anesthesia, emergency surgery, mortality, regional anesthesia.

airway As coronavirus disease (COVID-19), spread rapidly throughout the world on 11th of March 2020, it was announced to be a pandemic by World Health Organization [1]. SARS COV-2 is widely transmitted by droplets from person to person, by contact with infected objects, and by aerosol at a high viral concentration at a close distance. Since its high rate of transmission, the exposure to the disease and the risk of infection has increased for healthcare workers in centers where surgeries will be performed. In order to manage the pandemic period, in addition to the organization of hospital areas, personnel, and equipment, there was also a need to make a plan relating to patients to be taken into surgery. For this reason, a guideline in which suggests postponing elective surgeries during pandemic had been published by the American

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College of Surgeons and United States Department of Health and Human Services [2, 3]. In our country, the Ministry of Health has been declared several precautions in a statement to reduce the overload on health services with a directive dated 17/03/2020 with no 14500235-403.99, where authorities pointed out that elective surgeries should be postponed to a suitable time and be cautious about the availability of the beds in intensive care units [4]. Recommendations regarding anesthetic approaches applied to patients undergoing surgery during the pandemic process have been published. Therefore, the urgency of the operations and the anesthesia management of the patients have been changed.

The aim of our study is to examine our anesthetic approaches to surgical cases taken in our hospital in the early period of the COVID-19 pandemic.

METHODS

After obtaining approval of the local Ethics Committee (Approval number: 2011-KAEK-25 2020/05-06), the data of all surgical patients including general surgery (GS), orthopedics, neurosurgery (NS), urology, cardiovascular surgery (CVS), thoracic surgery, ear-nose-throat surgery (ENT) and plastic surgery (PRS) between 1 April 2020 and 20 May 2020 were retrospectively taken to the study. Patients with an ASA score I-IV diagnosed whether COVID-19, suspicious or not, underwent urgent and/or malignancy surgery were included. Polymerase Chain Reaction (PCR) tests were requested before all surgeries. However, emergency cases had to be taken without waiting for the results of PCR tests. All patients were taken to the operating room by measuring their fever and questioning the infection findings and coronavirus contact. The demographic data (age, gender, comorbidities, diagnosis), surgical indications, urgency, anesthesia management, and complications were evaluated. The anesthetic method used in the operation is examined as general anesthesia (GA), regional anesthesia (RA), regional anesthesia + sedoanalgesia (RSA), and sedoanalgesia (SA). The use of an endotracheal tube (ET) and laryngeal mask airway (LMA) during general anesthesia were recorded. Regional anesthesia included central neuraxial blocks (spinal, combined spinal-epidural, and epidural) and peripheral nerve blocks (interscalene, suprascapular, supraclavicular, infraclavicular, axillary, sciatic, femoral, and popliteal nerve blocks). Besides, patients' hospital stay period, intensive care unit (ICU) admission rate, 30 days mortality, and COVID-19 positivity after surgery were examined.

Statistical Analysis

Statistical evaluation is made by using SPSS 23.0 program. For numeric variables, descriptive statistics is defined as average ± standard deviation, and for data having a categorical structure they are defined in numbers and percentages. Results are evaluated in a confidence interval of 95%.

RESULTS

In our study, 290 patients in total are operated in a period of nearly two months in the surgery room of our hospital. In demographic data, there were observed that the number of female patients was less in all sur-

Table. 1. **Demographic data**

	General Surgery	Orthopedics	Neurosurgery	Urology	Cardiovascular Surgery
Age (year) (mean ± SD)	38.69 ± 15.85	44.42 ± 19.43	56.90 ± 13.39	55.17 ± 11.60	51.12 ± 17.36
F/M (n)	30/46	28/ 45	12/24	4/16	18/ 61
ASA I/II/III/IV (n)	8/12/4/2	0/0/0/0	0/10/6/0	0/ 3/7/ 0	0/0/0/0
ASAE I/II/III/IV (n)	15/20/9/6	14/39/14/6	0/10/7/3	0/ 4/ 6/ 0	3/10/46/20

F = Female. M = Male, ASA = American Society of Anesthesiologists

Table 2. Surgical indications of patients admitted for surgery

General surgery	Orthopedics	Neurosurgery	Urology	Cardiovascular Surgery
Appendectomy	Femur Fracture	Intracranial Tm	Bladder Ca	Coronary Bypass
Breast Ca	Subraconpylar Fracture	Aneurysm	DJ Stent	Dissection
GIS Perforation	Humerus Fracture	LDH	Nefrectomy	Embolectomy
Ileus	Amputation	CDH	Nephrolithiasis	EVAR
Stomach Ca		Shunt		Arterial injuries
Colon Ca		Subdural hematom		Pediatric CVS
Rectum Ca		Stabilization		
Mesenteric Ischemia		Decompression		
Thyroid Ca				
Perianal Abscess				

Ca = Cancer, LDH = Lumbar disc herniation, CDH = Cervical disc herniation, EVAR = Endovascular Aneurysma Repair, Tm =Tumor, DJ = Double J, CVF = Cardiovascular Surgery

gical branches (Table 1). The surgical indications of patients admitted during a pandemic period are shown in Table 2. CVS, Orthopedics, and GS were departments that admitted a most number of patients with ratios of 27.2%, 26.2%, and 25.2%, respectively. Patients undergoing emergency surgery were seen 79 patients in CVS, 73 patients in orthopedics, and 76 patients in GS. In anesthesia management, the application rates were GA 47.9%, RA 24.1%, RSA 9.0%, and SA 19.0%, respectively. The numbers of central nerve blocks were 11 combined spinal-epidural, 14 epidural, and 27 spinal blocks. All peripheral nerve blocks were performed with ultrasound guidance. If there was a motor branch of the nerve to be blocked,

Table 3. Type of surgeries and anesthetic approaches (n, %)

	290 n (%)	**Ca/ Emergency n (%) 50/240 (17.2/82.8)**	**ETT/LMA (n) 134/3**	**GA/RA/RSA/SA n (%) 139/70/26/55 (47.9/24.1/9.0/19.0)**
General Surgery	76 (26.2)	22 /54	55/0	55/6/15/0 (72.4/7.8/19.8/0)
Orthopedics	73 (25.2)	0/73	9/3	12/50/11/0 (16.4/68.5/15.1/0)
Neurosurgery	36 (12.4)	16/20	32/0	32/2/0/2 (88.8/5.6/0/5.6)
Urology	20 (6.9)	10/10	6/0	6/12/0/2 (30/60/0/10)
Cardiovascular Surgery	79 (27.2)	0/79	28/0	28/0/0/51 (35.4/0/064.6)
Ear Nose Throat Thoracic Surgery Plastic Surgery	6 (2.1)	2/4	6/0	6/0/0/0 (100/0/0/0)

ETT = Endotracheal tube, LMA = Laringeal mask airway, GA = General anesthesia, RA = Regional anesthesia, RSA = Regional anesthesia + Sedoanalgesia, SA = Sedoanalgesia

stimulation with a neurostimulator (Stimuplex Ultra, B Braun, Melsungen AG, Germany) was added to the ultrasound (Esaote, MyLab30Gold Cardiovascular, Florence, Italy) imaging. The numbers of upper extremity peripheral nerve blocks were 2 interscalene, 2 suprascapular, 4 supraclavicular, 11 infraclavicular, and 8 axillary blocks. The numbers of lower extremity nerve blocks were 15 sciatic, 9 popliteal, and 16 femoral blocks. In some situations, one of the peripheral nerve blocks or central neuraxial blocks could be combined with another nerve block or GA in the same patient. The application rates of regional anesthesia (with/without sedation) were 86.3% in orthopedics, 60.0% in urology, 27.6% in general surgery, and 0% in other surgeries (Table 3). Endotracheal intubation was performed in all patients except 3 child cases under general anesthesia. Laryngeal mask airway was used only in these cases in the orthopedics room. The average period of staying at the hospital was given in Table 4. 21% of total patients were admitted to ICU. The most number of ICU admissions were made in the CVS department. 30 days mortality rates as per surgical branches were determined as, 8.3% in NS, 6.6% in GS, 3.8% in CVS, and 2.7% in orthopedics. (Table 4). If the preoperative PCR test was negative, anesthesia was given. However, especially in emergency cases, some cases underwent surgery before the PCR test wasn't concluded. PCR tests were positive in the postoperative period in only 4 patients whose preoperative COVID-19 status was unknown. In 7 patients with a fever higher than 37.3°C at the preoperative period, then 2 patients of them had positive PCR test results postoperatively.

Hypotension was observed in 18 patients and bradycardia was seen in 13 patients perioperatively. Nausea and vomiting were observed in 14 patients postoperatively. Perioral cyanosis and metallic taste were seen in a patient who was administered sciatic and femoral nerve block. Methemoglobinemia (MetHb: 5.9%) was observed and treated with 6 l/min oxygen inhalation therapy and ascorbic acid 2g iv.

DISCUSSION

We evaluated our anesthesia approaches to 290 patients who were operated during the COVID-19 pandemic period, a total of 17.2 % malignancy and 82.8 % emergency patients were included. Our anesthesia approach was primarily planned according to the type of surgery and to prevent the transmission of COVID-19. In cases where GA was required to ensure airway safety, ETT was preferred instead of LMA to prevent particle contamination. RA was preferred whenever possible especially in orthopedic (83.6%) and urology (60.0%) patients.

Correctly defining surgical indications of patients during the pandemic period include importance both to avoid mortality relating to emergency cases and for correct organization of cancer patients during the process [4-6]. COVID-19 pandemic is an important public health disease with mortality and it requires a multidisciplinary approach relating to it. During treatment of patients for whom operation planning is made

Table 4. Durations of hospital stay, referral to intensive care unit and mortality rates

	Hospital stay (d) mean± SD	Referral to ICU n (%) 61 (21)	Mortality n (%) 13 (4.5)
General surgery	4.82 ± 4.12	15 (19.7)	5 (6.6)
Orthopedics	4.16 ± 2.06	6 (8.2)	2 (2.7)
Neurosurgery	4.6 ± 2.06	12 (33.3)	3 (8.3)
Urology	3.4 ± 2.12	0	0
Cardiovascular Surgery	7.24 ± 2.44	28 (35.4)	3 (3.8)
Ear Nose Throat Thoracic Surgery Plastic Surgery	3.15 ± 1.18	0	0

ICU = Intensive Care Unit

due to emergency or diagnosis of cancer, protection of health personnel and other patients, isolation of patient rooms, perioperative treatments and most importantly taking precautions for medical personnel, operating rooms, and surgical tools have significant importance [7, 8]. Chen *et al*. [9] recommended that surgical operations should be reduced to prevent cross-infection, non-surgical anti-tumor therapies should be chosen with higher priority if it is possible to recommend multidisciplinary therapies for malignant tumors, and neoadjuvant therapies for advanced gastrointestinal system malignancies. However, delaying of surgery for progressing disease would cause another public health crisis. For this reason, health service providers must consider the risks and benefits of malignancy surgery under these conditions [10]. With the announcement of pandemia, elective cases were delayed by complying with the directive of the Ministry of Health in the operating room of our hospital. By reducing a number of operating rooms, recommended arrangements were made. Emergency (82.8 %) and cancer patients(17.2 %) were taken into operations.

The first step of anesthesia planning for a patient during COVID-19 pandemic period is to determine whether COVID-19 test of a patient comes out to be negative, positive, or suspicious positive. When the spreading of disease is considered, until it is proven otherwise, all patients should be deemed to be positive [11]. A preoperative coronavirus PCR test was performed on cancer patients and emergency patients scheduled for surgery in our hospital. Emergency patients underwent surgery without waiting for the PCR test results and were taken into operation pretending to be positive. Emergency patients whose PCR test was not completed were taken to surgery in the negative pressure operating room. All patients were taken to the operating room by measuring their fever and questioning the infection findings and coronavirus contact in our hospital. In all patients, 7 patients had a fever higher than 37.3°C, and only 2 of them had positive PCR test results postoperatively. Since every patient was considered to be positive for COVID-19 and all precautions were taken against COVID-19 preoperatively and intraoperatively, health workers were not infected.

Planned anesthesia method should be the most appropriate technique for patient and surgery type carrying a minimum risk of viral transmission for the perioperative intervention team. The American Society of Regional Anesthesia and Pain Medicine and the European Society of Regional Anesthesia and Pain Therapy have recommended neuraxial anesthesia and peripheral nerve blocks for patients with COVID-19. If it is possible to use RA, it should be the primary anesthesia method that is preferred. In addition to postoperative pain control, RA can prevent pulmonary complications and viral transmission. Usage of RA is not contraindicated for COVID-19 positive and suspicious patients [12, 13]. A good planning should be made for the operation to be performed with RA. In the intraoperative period having a requirement to turn back to GA in an unexpected way would be the least desired situation [14]. In the study of Price *et al*. [15], which included 100 emergency orthopedic patients during the COVID-19 period, 70% (n = 70) general anesthesia and 30% (n = 30) regional anesthesia were applied. Although our RA rate was 33.1% totally, our RA according to surgical branches was applied to 83.6% of orthopedic patients and 60.0% of urology patients. Axillary or infraclavicular brachial plexus block instead of superior truncus block (supraclavicular and interscalene) should be preferred. Potential complications specific to brachial plexus blocks include pneumothorax and phrenic nerve injury, which can cause further respiratory failure in the COVID-19 patient [16]. For these reasons, we preferred infraclavicular and axillary blocks in 76.0% of the upper extremity blocks in orthopedic cases.

Airway management during general anesthesia causes aerosol emission, exposing the healthcare team to the increased risk of COVID-19 transmission during both intubation and extubation. It is known that the probability of acute respiratory tract infection transmission to a healthcare professional during tracheal intubation is 6.6 times higher than those who do not have tracheal intubation [17]. The Anesthesia Patient Safety Foundation (APSF) and the American Society of Anesthesiologists (ASA) recommend rapid sequence induction and intubation because of the risk of supraglottic airways (e.g. laryngeal mask) generating more aerosols compared to tracheal intubation [18, 19]. Preoxygenation was achieved by applying 100% O_2 for 3-5 minutes with a face mask before anesthesia to our patients who are given general anesthesia. In these patients, it was avoided ventilation with a mask. An endotracheal tube was applied with rapid serial in-

duction using analgesia and muscle relaxants. The laryngeal mask was used in 3 children patients who required mask ventilation in which sedoanalgesia was insufficient.

Operating rooms are high-risk areas concerning transmission by airway or contact. For this reason, it is recommended that all surgical procedures be performed in a negative pressure room, if available [20]. Although operating room systems in our country are generally well designed to deal with such high-risk situations, the high risk of transmission and prevalence of the disease, limited resources, heavy workload, greatly increase the risk of COVID-19 transmission to the operating room team. In the management of surgical patients worldwide, anesthesiologists encounter more cases of COVID-19 cases. To minimize all these risks, all the necessary equipment for anesthesia and surgery was prepared in our hospital. Doctors, nurses and staff were trained. Materials such as monitors and ultrasound devices were protected with a transparent cover, protective personal equipment(PPE) for the team was worn in accordance with the instructions.

Concerning postoperative complications and mortality, it is important whether surgical intervention is urgent or malignancy. In a study, conducted it was emphasized that emergency surgical application is an important indicator in predicting mortality risk [21]. Emergency abdominal surgery has worst results and high death rates when compared with elective surgery. In the studies conducted at normal times 30 days mortality was determined as 3.8-5% in general surgical GS cases, it was determined as 0.92% in orthopedics, as 1.9-5.3% in CVS and as 2.6% in NS [22-25]. Changes in mortality rates have been investigated in some studies during the COVID-19 pandemic period. In a study in orthopedic patients in the early period of the COVID-19 pandemic, they reported the overall 30-day mortality rate was 3% [15]. In another study involving 153 emergency general surgery patients during the surge of COVID- 19 pandemic, they found a 30-day mortality rate of 7% [26]. Grassner *et al*. [27] examined emergency neurosurgical procedures during the first wave of the pandemic, they found that the 30-day mortality did not increase compared to the previous 4 years (between 4,5%-8,9%). They stated that decreased incidence of neurosurgical emergency and this was related to the restrictions placed on mobility within countries [27]. In our study, the mortality rates were seen as 8.3% in NS, 6.6% in GS, 3.8% in CVS and 2.7% in orthopedics. We consider that operations admitted in NS due to tumor surgery and emergency intervention to hemorrhagic cerebrovascular events. GS department during COVID-19 pandemic period generally included malignities that might cause metabolic disfunction and therefore they had higher mortality rate. In the postoperative period, PCR tests were positive in 4 patients. Two of them were hospitalized in ICU and were died during their follow-up. We think that the type of surgery performed and the presence of comorbid diseases in these patients are effective in their mortality. The other covid positive patients were treated in their clinics.

CONCLUSION

We think that the correct and timely selection of surgical indications and the planning of the process with protective anesthesia approaches for the patient and healthcare personnel may affect morbidity and mortality in the early covid 19 pandemic period. As a result surgical operations and anesthetic approaches were performed in accordance with the guidelines, and the correct usage of beds and ICU capacity of our hospital was ensured and the mortality rates were kept at normal levels. In cases where anesthesia can be managed with RA during the Covid-19 pandemi period, we recommend that RA be applied firstly if there are no contraindications.

Authors' Contribution

Study Conception: ÜK; Study Design: ÜK; Supervision: ÜK, FA; Funding: ÜK, CY; Materials: FA, CY; Data Collection and/or Processing: ANB; Statistical Analysis and/or Data Interpretation: ÜK; Literature Review: TO; Manuscript Preparation: ÜK, FA and Critical Review: CY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Arthroscopic treatment and mid-term results of suprapatellar plica syndrome: a single-center experience of 14 cases

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ABSTRACT

Objectives: Synovial plicae syndrome (SPS) are encountered as a mesenchymal tissue remnant during the process of embryological development, and divide the knee joint into three separate compartments. Of these, the suprapatellar plica may be affected by a syndrome that manifests with anterior knee pain, a clicking sound, snagging and a feeling of skipping after a patellofemoral overload. The present study evaluates 14 patients with suprapatellar complete plica syndrome who were treated between 2013 and 2019, and discusses the medical and surgical medium-term results of the condition.

Methods: Included in the study were 225 cases who underwent knee arthroscopy between 2013 and 2019, the data of which were analyzed retrospectively. The exclusion criteria were accompanying meniscal tear, anterior and posterior cruciate ligament tears, chronic inflammatory arthritis, varus > 3˚ and valgus > 5˚ malalignments. The cases were followed-up using the Tegner Lysholm knee scoring method, during the preoperative period, in the postoperative period, and in postoperative week 12 and month 6. The statistical analysis was performed using the IBM SPSS Statistics (Windows Version 25.0. Armonk, NY: IBM Corp.) software package.

Results: A retrospective analysis revealed a BMI of 28.7 ± 5.6 kg/m2 in the 14 cases. The mean age was 34.57 ± 8.53 years. Intraarticular cortisone injections and intraarticular viscosupplementations were performed at the outpatient follow-up in eight and three cases, respectively. Furthermore, eight cases had undergone previous physical therapy and rehabilitation. The mean duration of symptoms was 1.4 ± 0.8 months. The Tegner Lysholm knee scores were 69.53 ± 6.15, 88.23 ± 3.00, and 93.76 ± 3.83 in the preoperative period, week 12 and month 6, respectively.

Conclusions: In conclusion, arthroscopy can be considered an efficacious and diagnostic method in knee plica syndrome. Patient satisfaction is high in the medium-term.

Keywords: Suprapatellar plica syndrome, knee joint, arthroscopy

Suprapatellar syndrome (SPS) usually presents in the third decade of life, [1-2] with complaints of anterior knee pain, cracking noises, stumbling feelings and a popping sensation after patellofemoral overloading [2-5]. The prevalence of SPS varies in different populations, although the general prevalence worldwide is 10% [2, 3, 6, 7]. Suprapatellar syndrome is classified as suprapatellar, mediopatellar, infrapatellar and lateral, depending on the anatomical location (Fig. 1), while the most common type is medial plica [2, 3, 6, 7].

Plica, in its normal state, is a thin, flexible and

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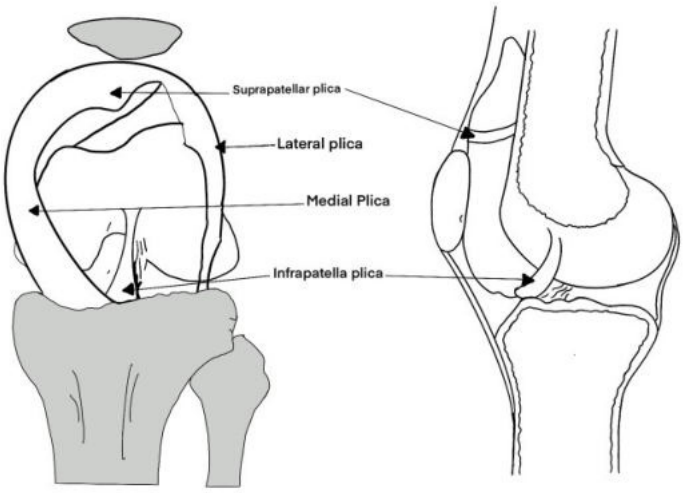

Fig. 1. Representative drawing of a suprapatellar, medial, infrapatellar and lateral plica of the knee.

transparent structure, and is associated with such mechanical complaints as pinching between the quadriceps tendon at the range of motion of the knee at 70-100 degree flexion, depending on the position of the plica.

Many SPS cases are idiopathic, and almost 60% are bilateral [7]. Other causes are generally trauma, overuse, hematoma, diabetes mellitus and inflammatory arthropathy.

A total of 14 cases with suprapatellar complete plica syndrome who presented to our hospital between 2013 and 2019 were evaluated in the study, in which and medium-term medical and surgical results are discussed.

The aim of this study is to discuss the success of arthroscopic surgery in suprapatellar plica syndrome. We believe that such a arthroscopic surgery will be a guide in the treatment of future patients, since patients with suprapatellar plica syndrome are mostly involved in terms of the characteristics of our hospital.

METHODS

Involved in the present study were 225 patients that underwent knee arthroscopy between 2013 and 2019, whose data were analyzed retrospectively. The exclusion criteria were accompanying meniscal tear, anterior and posterior cruciate ligament tears, chronic inflammatory arthritis, varus > 3˚ and valgus > 5˚ malalignments. The number of cases with no active pathological or anatomical findings other than plica syndrome and that underwent knee arthroscopy was 44, according to the evaluations performed; 30 cases had a medial, lateral or infrapatellar plica; and a suprapatellar plica was present in 14 cases. Retrospective screening revealed a BMI of 28.7±5.6 kg/m2 among the 14 cases included in the study, in which the mean age was 34.57 ± 8.53 years. Intraarticular cortisone injections and intraarticular viscosupplementations were performed at outpatient follow-up in eight and three cases, respectively. Furthermore, eight cases were found to have undergone physical therapy and reha-

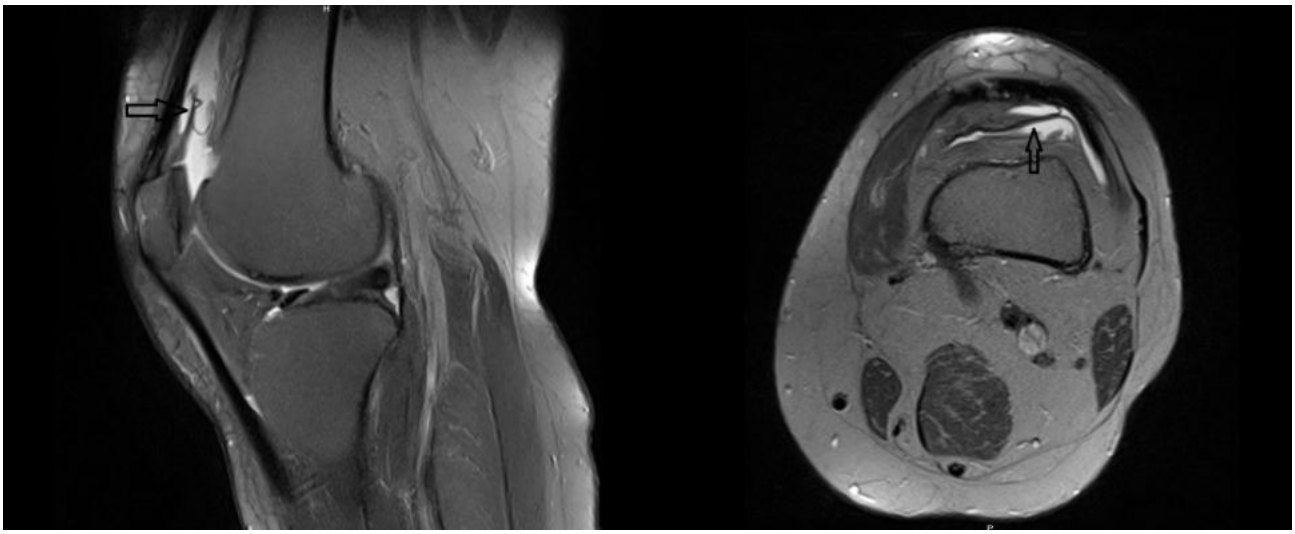

Fig. 2. Suprapatellar plica in the Sagittal and Transverse planes on MR measurement (black arrow).

Table 1. Characteristic features of the cases.

Cases	Age	Intraarticular cortisone injection	Intraarticular Viscosupplementation	Physical therapy and rehabilitation previously	Knee pain	Clicking sound	Locking	Complications
1	32	-	-	+	+	-	+	-
2	34	-	-	+	+	-	+	-
3	36	+	-	+	+	+	+	-
4	40	+	-	+	-	-	+	-
5	23	-	-	-	-	-	+	-
6	22	-	-	-	-	+	+	-
7	43	+	+	+	-	+	+	-
8	47	+	+	+	+	-	+	+
9	45	+	-	-	+	-	+	-
10	29	-	-	-	-	+	-	-
11	35	+	-	-	+	-	+	-
12	39	+	+	+	+	-	+	-
13	39	+	-	+	+	-	+	-
14	20	-	-	-	-	+	+	-

bilitation previously. The mean duration of symptoms of the cases was 1.4 ± 0.8 months. The most frequent complaints were knee pain in eight cases, a clicking sound in six cases, a sense of stumbling or locking at over-flexion of the knee in 13 cases and a sense of popping after patellofemoral overload in 14 cases (Table 1). Plica syndrome was observed as an accompanying MRI finding in 10 cases (Fig. 2).

Written and verbal consent was obtained in all cases, and approval for the study was obtained from the Nigde Omer Halisdemir University, School of Medicine, Non-Interventional Clinical Research Ethics Board was taken.

Surgical Technique

The surgical field was entered via the standard antero-lateral port under spinal or general anesthesia and after a tourniquet application, scrubbing and draping. The antero-medial port was entered from the exterior to interior under direct vision. An arthroscopic exam-

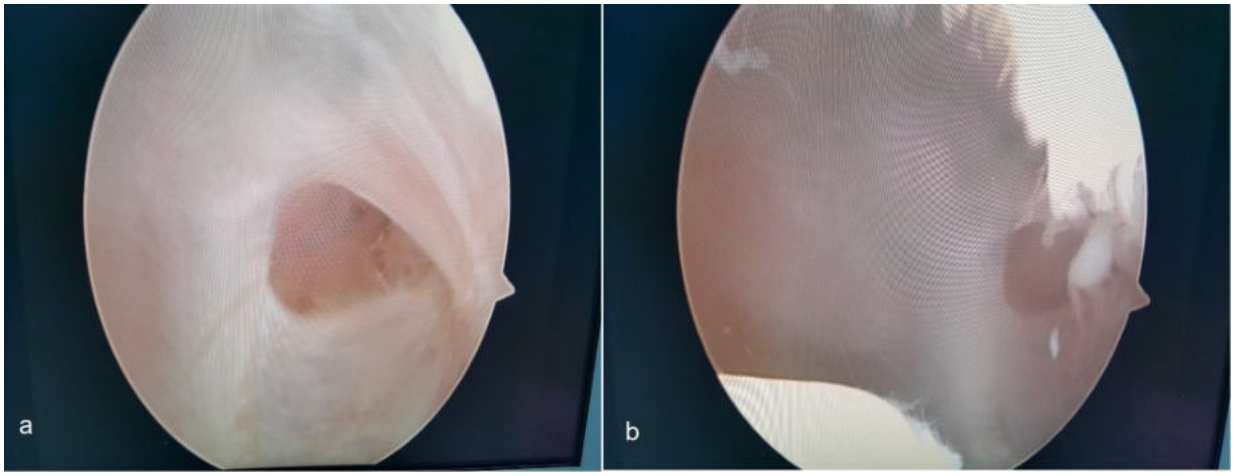

Fig. 3. (a) Suprapatellar plica during arthroscopy, (b) Suprapatellar space after debridement by arthroscopic tools.

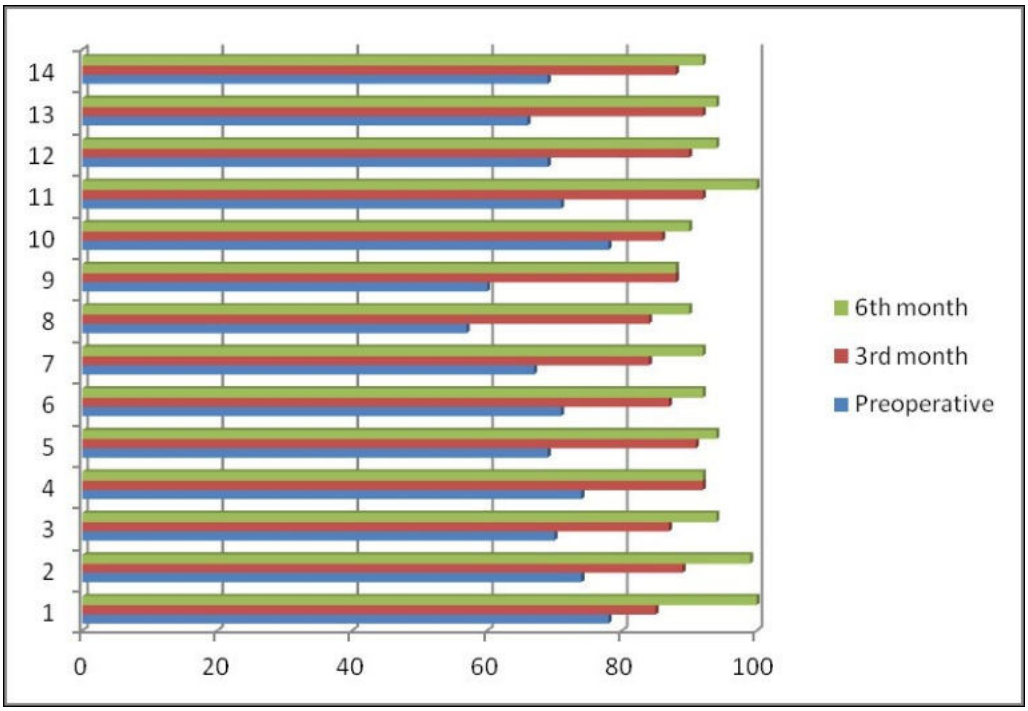

Fig. 4. Distribution of the cases according to the Tegner lysholm score preoperatively, at 3 and 6 months.

ination revealed an intact medial and lateral meniscus, anterior and posterior cruciate ligaments and cartilage tissues. A suprapatellar plica was observed and was released, and a debridement was performed (Fig. 3). A drain was placed and the skin was sutured. The wound was dressed and a Jones bandage was applied, and the sutures were removed on the postoperative 15th day. A superficial skin infection developed on postoperative 6th day in one case and was treated with oral antibiotics. No serious complications developed in the remaining cases, other than the above.

Statistical Analysis

The cases were followed-up based on the Tegner Lysholm knee scoring method, applied during the preoperative period, postoperative period, and postoperative week 12 and month 6 [8]. Statistical analysis was performed using IBM SPSS Statistics (Windows Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

The Tegner Lysholm knee scores of the cases were 69.53 ± 6.15, 88.23 ± 3.00 and 93.76 ± 3.83 in the preoperative period, at week 12 and month 6, respectively. Significant differences were noted in the three control groups when the preoperative, week 12 and month 6 Tegner Lysholm knee scores were compared ($p < 0.05$) (Fig. 4).

DISCUSSION

Plica syndrome of the knee is a commonly problem of the knee in the adult population. The condition is frequently confused with osteochondritis dissecans, meniscal tears and degeneration, and patellar alignment disorders. Magnetic resonance imaging is a useful approach to differential diagnosis, although the sensitivity and specificity of axial MRI imaging, sagittal sections, and both sections when evaluated together are 73% and 78%, 71% and 83%, and 95% and 72%, respectively [9]. As such, it is necessary to consider additional pathologies in a differential diagnosis in cases involving plica syndrome.

Isolated plica cases may frequently be overlooked by clinicians during routine evaluations. A thickened plica can be palpated 1 cm medial to the upper pole of the patella in medial plica syndrome, and some patients might feel pain on palpation in the plica region as a result of this synovial thickening. Hughston's

plica test and the Stutter test are provocative tests for plica syndrome, and may be applied concomitantly in physical examination [10-13].

The most reliable method in the treatment is arthroscopy, although intraarticular cortisone injections are also applied for the treatment of plica syndrome, being an efficacious diagnostic method and a highly detailed approach to treatment applied by clinicians [1, 2]. A clear view of the lesion and intervention allows a 100% diagnosis, as was the case in this present study in which a significant difference was found in the Tegner-Lysom scores between the preoperative and postoperative periods, indicating clinical improvement. Tegner-Lysom is important to measure both function and activity level [8] and Also It has good criterion validity and test-retest reliability.

Limitations

The most significant limitation of the present study is its retrospective design, while further limitations include the small sample size and the fact that no MRIs were obtained postoperatively, as a follow-up MRI, after clinical improvement is considered unethical. The short duration of follow-up is another limitation of the study.

CONCLUSION

Arthroscopy can be considered an efficacious treatment and diagnostic approach in knee plica syndrome. Patient satisfaction is high in the short and medium term.

Authors' Contribution

Study Conception: MA, SÇ; Study Design: MA; Supervision: MA; Funding: MA, SÇ; Materials: MA; Data Collection and/or Processing: MA, SÇ; Statistical Analysis and/or Data Interpretation: MA; Literature Review: SÇ; Manuscript Preparation: MA, SÇ and Critical Review: MA, SÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The effect of psychopathology on quality of life and disability in patients with fibromyalgia

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ABSTRACT

Objectives: The aim of the study was to investigate the relationship between pain, depression, anxiety, somatic amplification and alexithymia in patients with fibromyalgia syndrome (FMS), and on quality of life and disability. As a secondary goal, the predictors of disability were evaluated.

Methods: Participants were 112 female patients aged 18 and over, applied to the outpatient clinic of University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Medical Ecology and Hydroclimatology department and diagnosed with FMS according to ACR 2016 Revised Fibromyalgia Diagnosis Criteria. The Sociodemographic Data Form, Visual Analog Scale (VAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Toronto Alexithymia Scale (TAS-20), Somatosensory Amplification Scale (SSAS), Fibromyalgia Impact Questionnaire (FIQ) and Health Survey Questionnaire Short Form (SF-36) were applied to each participant. All data were analyzed with correlation and linear regression.

Results: Increased pain intensity, depression, anxiety, somatic amplification, "difficulty identifying feeling" and "difficulty describing feelings" dimensions of alexithymia were found related to lower quality of life and increased disability. Depression, somatic amplification, and pain severity were defined as the predictors of disability in FMS.

Conclusions: Psychiatric examination of FMS patients especially in terms of depression, anxiety, alexithymia and somatic amplification as well as their physical complaints can be beneficial to minimize disability and increase the quality of life. To our best knowledge, this is the first study to show somatic amplification as a predictor of disability in FMS patients. Further studies will be helpful to understand this relationship.

Keywords: Alexithymia, anxiety, depression, fibromyalgia syndrome, quality of life, somatization

Fibromyalgia syndrome (FMS) is a chronic pain condition characterized by widespread body pain and excessive tenderness at specific body sites, and causes adverse effects on quality of life. FMS causes reduced functional capacity and difficulties in the fulfillment of daily life activities. Severe pain, the main symptom of the disease, causes reluctance and disability and negatively affects the functionality of the person [1, 2].

The etiology of FMS is not yet well-known. A significant part of the studies conducted to explain the etiology is on the relationship between psychiatric dis-

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orders and FMS [3]. Depression is the most comorbid psychiatric disorder with FMS. It has been shown that depressive symptoms increase as the pain severity and duration of pain increases [4, 5]. One of the psychiatric symptoms most frequently seen in patients diagnosed with FMS is anxiety. It has been suggested that FMS patients with high anxiety symptoms show decreased physical activity and sedentary behaviors [6].

Alexithymia is defined as a disability to recognize one's own and other people's emotions. Taylor *et al*. [7]) reported that alexithymic personality traits were widely observed in FMS. Although depressive or anxiety symptoms of FMS patients are evident, they often seek help due to their widespread pain. This is thought to be due to the patients' inability to understand and express their emotions [7, 8]. Lumley *et al*. [9] suggested that alexithymic individuals may tend to misinterpret their emotional state as a sign of physical illness.

Alexithymia has also been associated with somatization as well as depression and anxiety [10]. Somatization concept defined as the person, experiencing and expressing physical/somatic symptoms that do not have a pathophysiological explanation, has a tendency to misinterpret them as a sign of illness and seek medical remedies [11]. It is well-known that somatic amplification is higher in various chronic pain syndromes such as headache, migraine, osteoarthritis, low back pain, neck pain, including FMS compared to healthy controls [12].

As a result, pain, depression, anxiety, alexithymia and somatic amplification may be related to each other and affect quality of life and disability in FMS patients. To the best of our knowledge, there is no study that evaluated these variables together in FMS patients. Thus, in this study, the aim was to investigate the relationship of pain, depression, anxiety, somatic amplification and alexithymia with each other, quality of life and disability in patients with fibromyalgia syndrome (FMS). In addition, secondary aim was to evaluate the predictors of disability.

METHODS

Participants

The study included 112 female patients who applied to the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Medical Ecology and Hydroclimatology Clinic between September 2018 and April 2019 with widespread pain and diagnosed with FMS according to the American College of Rheumatology 2016 Revision Fibromyalgia Diagnostic Criteria [13]. Other inclusion criteria were: (1) 18-over age, (2) being literate, (3) volunteering to study. Exclusion criteria were: (1) mental disability/retardation, (2) neuro-cognitive disorders, (3) other organic mental disorders. All patients signed informed consent before participation. The tests were given in a single session with a randomized order. Prior to the research, ethics committee approval was obtained from University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee on 25.07.2018 numbered 2011-KAEK-25 2018/07-02.

Instruments

Demographic Data Form

The researchers developed a form to obtain sociodemographic data from the participants based on the objectives of the study.

Visual Analog Scale (VAS)

The scale developed by Price *et al*. (1983) measures the severity of the pain that the patient experienced [14]. The test consists of a 100 mm long straight line with the endpoints defining extreme limits: no pain to extreme pain. The patient required to mark the severity of his/her pain level between the two endpoints.

Beck Depression Inventory (BDI)

BDI is a 21-item self-report inventory that measures the risk for depression and depressive symptoms [15]. The standardized Turkish form was used as a valid and reliable measurement [16]. Participants were asked to rate how they had been feeling for the last week. Higher total scores indicate more severe depressive symptoms.

Beck Anxiety Inventory (BAI)

BAI is again a 21-item, self-report inventory that is used for measuring the severity of anxiety levels. It questions the symptoms that the patient has experienced the last week. Higher total scores indicate more severe anxiety symptoms. The standardized Turkish

form was used [17, 18].

Toronto Alexithymia Scale (TAS-20)

TAS is a 20-item, self-report scale as one of the most commonly used measures of alexithymia. Participants were required to rate using a 5-point likert scale from 1=strongly disagree to 5=strongly agree. TAS has three subscales: (1) Difficulty Describing Feelings, (2) Difficulty Identifying Feelings, and (3) Externally Orienting Thinking. The standardized Turkish form was used to assess alexithymia levels of the patients [19, 20].

Somatosensory Amplification Scale (SSAS)

SASS is a simple and quick (requires less than 10 minutes) instrument designed to assess somatic and visseral sensations. It allows clinicians to evaluate somatosensory amplification in various diseases with fewer questions. SASS asks participant how much s/he experiences various uncomfortable somatic and visseral sensations most of which are not symptoms of a serious disease pathology. The valid and reliable Turkish form was for the assessment [21, 22].

Health Survey Questionnaire Short Form (SF-36)

It is a 36-item, self-report survey that questions the quality of life (QOL) especially in patients with physical illness. SF-36 consists of eight subscores: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health [23]. Scores for each domain are calculated by a scoring key and a total scoree indicating the level of QOL. The total scores range between 0-100 and lower scores represent the more severe disability. We used the valid and reliable Turkish form [24].

Fibromyalgia Impact Questionnaire (FIQ)

It is a 10-item, self-report instrument to measure FM patient status, progress and outcomes [25]. It only takes five minutes to complete and requires the participant to mark their experience. It is used to measure self-feeling, pain, fatigue, inability to work, difficulty at work, snails, morning fatigue, anxiety and depression. The first item includes 11 4-point Likert scale questions about physical functioning. Items 2-3 ask the patient the number of days they felt well and unable to work due to FM symptoms. Items 4-10 measure work difficulty, morning triedness, stiffness, anxiety, depression, pain and fatigue. The scores of each domain range from 0 (no impairment) to 10 (maximum impairment) and total score is maximum 100. Lower scores mean less effect of the disease. The standardized Turkish form was applied [26].

Statistical Analysis

All collected data were analyzed by SPSS 18.0 Windows package program. The normal distributions of continuous variables were examined with Saphiro-Wilk test. Pearson r correlation was used for normally distributed parameters whereas Spearman correlation was preferred for non-normally distributed parameters to analyze inter-scale relationships. Numeric variables were presented with values corresponding to mean ±

Table 1. Demographic and clinical characteristics of study sample (n = 112)

	n (%) Mean ± SD Median (Min-Max)/
Age (years)	45.0 ± 10.1
Length of education (years)	5 (5-20)
Marital status	
Single	21 (18.8)
Married	91 (81.2)
Working status	
Working	31 (27.7)
No job	81 (72.3)
Socioeconomic status	
Low	24 (21.4)
Middle/high	88 (78.6)
BMI	27.0±5.0
Height (m)	1.60 (1.45-1.78)
Weight (kg)	68 (50-126)
Psychiatric treatment history	
Yes	70 (62.5)
No	42 (37.5)
Comorbid medical conditions	
Present	48 (42.9)
None	64 (57.1)

BMI = Body Mass Index

standart deviation (mean ± SD) or median (Min-Max), while categorical variables were presented with the number of observations and percentage (n-%) notations. The alpha levels were < 0.05 and < 0.01 depending on the analysis. To test hypothesis, linear regression analysis was used.

RESULTS

Demographical and Clinical Data

Our study included 112 female FMS patients (mean age= 45.00 ± 10.10 years). Demographic and clinical characteristics of participants are given in Table 1 and scale scores are in Table 2.

The VAS scores had significant positive correlations with BDI (r = 0.42, $p < 0.01$), BAI (r = 0.42, $p < 0.01$), TAS-20 difficulty identifying feelings subscale (r = 0.29, $p < 0.01$), TAS-20 difficulty describing feelings subscale (r = 0.23, $p < 0.05$), TAS-20 total scores (r = 0.39, $p < 0.01$), FIQ (r = 0.62, $p < 0.01$) and SASS (r = 0.24, $p < 0.01$).

The FIQ scores had also showed positive correlations with BDI (r = 0.58, $p < 0.01$), BAI (r = 0.59, $p < 0.01$), TAS-20 difficulty identifying feelings subscale (r = 0.49, $p < 0.01$), TAS-20 difficulty describing feelings subscale (r = 0.27, $p < 0.01$), TAS-20 total score (r = 0.40, $p < 0.01$), and SSAS (r = 0.42, $p < 0.01$).

The SASS scores had significant positive correlations with BDI (r = 0.40, $p < 0.01$), BAI (r = 0.60, $p < 0.01$), TAS-20 difficulty identifying feelings subscale (r = 0.46, $p < 0.01$), TAS-20 difficulty of describing feelings subscale (r = 0.32, $p < 0.01$) and TAS-20 total (r = 0.40, $p < 0.01$) besides VAS and FIQ.

The comparisons between SF-36 and VAS, FIQ, BDI, BAI, TAS-20, SSAS was reported in Table 3.

Predictors of FIQ

Linear regression analysis was performed to test the effects of demographic, clinical characteristics,

Table 2. Scores obtained by participants from the scales (n = 112)

	Mean ± SD Median (Min-Max)/
BDI	18.9 ± 10.6
BAI	23.5 (0-59)
VAS	58.9 ± 21.5
FIQ	54.4 ± 19.5
SSAS	30.2 (10-48)
TAS-20 Difficulty identifying feeling	18 (7-35)
TAS-20 Difficulty describing feelings	14 (5-25)
TAS-20 Externally-oriented thinking	21 (8-30)
TAS-20 Total	53.6 ± 12.4
SF-36 Physical functioning	60 (0-100)
SF-36 Role function (physical)	25 (0-100)
SF-36 Pain	50 (0-90)
SF-36 General health	55 (20-85)
SF-36 Vitality	50 (15-80)
SF-36 Social functioning	50 (0-87.5)
SF-36 Role function (emotional)	33.3 (0-100)
SF-36 Mental health	52 (24-72)

BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, VAS = Visual Analog Scale, FIQ = Fibromyalgia Impact Questionnaire, SSAS = Somatosensory Amplification Scale, TAS-20 = Toronto Alexithymia Scale, SF-36 = Health Survey Questionnaire Short Form

Table 3. Relationship between SF-36 and VAS, FIQ, BDI, BAI, TAS-20, SSAS scores in the study sample (n = 112)

	SF-36							
	Physical functioning	Role function (physical)	Pain	General health	Vitality	Social functioning	Role function (emotional)	Mental health
	r	r	r	r	r	r	r	r
VAS	-.44**	-.37**	.57**	.19*	-.13	.03	-.39**	-.37**
FIQ	-.54*	-.54*	.65*	.16	-.04	.10	-.54*	-.31*
BDI	-.42**	-.27**	.36**	.10	.08	.22*	-.35**	-.40**
BAI	-.54**	-.35**	.44**	.14	-.06	.22*	-.46**	-.38**
SSAS	-.42**	-.26**	.34**	-.05	-.05	.11	-.37**	-.15
TAS-20 difficulty identifying feeling	-.34**	-.18	.32**	.00	-.00	.14	-.37**	-.31**
TAS-20 difficulty describing feelings	-.23*	-.11	.20*	.01	.12	.25**	-.25**	-.27**
TAS-20 externally-oriented thinking	.05	.05	-.04	.07	.00	.03	.01	.06
TAS-20 Total	-.29**	-.15	25**.	.04	.02	.18*	-.32**	-.28**

SF-36 = Health Survey Questionnaire Short Form, VAS = Visual Analog Scale, FIQ = Fibromyalgia Impact Questionnaire, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, SSAS = Somatosensory Amplification Scale, TAS-20 = Toronto Alexithymia Scale

VAS, BDI, BAI, SSAS, TAS-20 scales on FIQ scores. The predictors of the model were significant FMS duration ($p < 0.05$), VAS, BDI, BAI, SSAS, TAS-20 difficulty identifying feelings. The analysis was performed via "backward stepwise" method. Respectively, following predictors were eliminated: FMS duration in step 2, BAI in step 3, TAS-20 difficult identifying feeling in step 4. As a result, the regression model was statistically significant ($F = 46.771$, $p < 0.01$). FIQ increased by 0.419 units ($\beta = 0.419$, $p < 0.01$) when VAS increased by one unit, FIQ increased by 0.419 units ($\beta = 0.655$, $p < 0.01$) when BDI increased by one unit, and FIQ increased by 0.388 units ($\beta = 0.655$, $p = 0.020$) when SSAS increased by one unit. VAS, BDI, SSAS can explain 0.553 variance of FIQ (Table 4).

DISCUSSION

In the present study, the binary relationships between pain, depression, anxiety, somatic amplification and alexithymia, and their relationships with quality of life and disability were examined in patients with FMS. It was found that depression, somatic amplification and pain severity were the predictors of disability.

The findings also showed that pain severity was

Table 4. Predictors of FIQ

Dependent variable	Independent variable	β	*p* value	Model (*p*)
FIQ	Constant	5.645	0.287	**< 0.01**
	VAS	0.419	**< 0.01**	
	BDI	0.655	**< 0.01**	
	SSAS	0.388	**0.020**	

Linear regression, $p < 0.01$, Adjusted R Square = 0.553, FIQ=Fibromyalgia Impact Questionnaire, VAS = Visual Analog Scale, BDI = Beck Depression Inventory, SSAS = Somatosensory Amplification Scale

positively correlated with depression, anxiety, alexithymia and somatic amplification. Pain severity was also positively correlated with worsening quality of life and increased disability. Besides pain negatively affects quality of life, it also has negative effects on mood, sleep patterns, daily work and activities, mental state and vitality [27]. It has been reported that pain is the most important predictor of quality of life and disability in FMS patients [28].

Participants in our study had mild-moderate depressive symptoms and moderate-severe anxiety symptoms. The most common psychiatric disorders in FMS are depression and anxiety disorders. Comorbidity of depression, anxiety and FMS that have common pathophysiology and respond to similar treatments led to the view of a single underlying condition of depression, anxiety and FMS appears with different symptoms [29]. It has been suggested that somatoform diseases, including FMS, and depression comorbidity are associated with all functionality and quality of life indices, while reporting that anxiety has a relatively narrower effect [30]. It has been found that depression is an important predictor especially for SF-36 vitality and mental health subscales and FIQ, while anxiety is a predictor of SF-36 general health, social role functioning, mental health and emotional role difficulties [28].

We also found a positive correlation between pain severity and depression and anxiety. The presence of depression and/or anxiety in FMS patients is a factor to increase pain severity. A study compared the pain and symptom severity of FMS patients with and without depression and found that patients with depression had experienced more severe pain compared to non-depressed patients. In the same study, it was also evident that pain severity was higher in FMS patients with anxiety compared to patients without anxiety. The study reported that the existence of depression and anxiety in chronic pain conditions was associated with more severe pain, disability and lower quality of life [31]. The relationship between pain, depression and anxiety was explained by psychological mechanisms. Hypervigilance and catastrophe may mediate the relationship between these three states by increasing the physical and psychological symptoms of the patient. Thus, it has been stated that the one's perception of pain may increase in the context of depression and anxiety [32].

Findings on the relationship of somatic amplification in chronic pain conditions with QOL and disability are limited. It has been reported that increase in somatic symptom burden has negative effects on QOL in patients with chronic lumbar pain [33]. Moreover, It has been stated that somatic amplification has a significant effect on disability of patients with chronic lumbar pain whereas it has no effect on QOL and disability of patients with chronic neck pain [34, 35]. It was also shown that somatization is associated with intensity of pain, functional status and recovery perception in patients with chronic lumbar pain [36]. Additionally, somatization and pain disaster had negative effects on pain and QOL through alexithymia on patients with headache [37].

As far as we know, our study is the first to evaluate the effect of somatic amplification on QOL and disability in FMS. We found that somatic amplification has negative impact on QOL of FMS patients, especially in physical and emotional situations. The regression analysis showed that somatic amplification is also a predictor of disability in FMS. Negative effects of somatization on QOL and disability in FMS patients can be explained the fact that the impact of somatization on decreased physical activity of the individual, the duration of pain, depression and its relationship with alexithymia. Further studies are needed to explore the mechanism of how somatization affects the QOL and disability in patients with FMS. Further study is needed on the mechanisms through which somatization effects on quality of life and loss of ability in patients with FMS.

We also found that the two dimensions of alexithymia, "difficulty identifying feelings" and "difficulty describing feelings" have negative effects on the physical and psychological dimension of QOL and relate to disability. Alexithymia increases pain sensitivity and emotional pain experience. It has been suggested that alexithymia has adverse effects on psychosocial and physical dimension of QOL by mediating psychiatric symptoms [38]. Another study also argued that alexithymia negatively affects QOL through depression and other psychiatric disorders. Additionally, they suggested that people with alexithymic characteristics experience more difficulties in identifying and describing emotions and thus, perceive emotions as a somatic symptom, so alexithymia is a predisposing factor for somatization [39]. In our study,

the negative effect of alexithymia on pain may have affected the QOL of FMS patients through psychiatric effects and somatic amplification.

CONCLUSION

We investigated the factors affecting QOL and disability in FMS. The findings showed that pain severity, symptoms of depression and anxiety and somatic amplification, "difficulty identifying feeling" and "difficulty describing feelings" dimensions of alexithymia have impacts on QOL and disability and pain severity, depression and somatic amplification are the predictors of disability of FMS patients. The present study is the first to show somatic amplification as a predictor of disability in FMS patients. Further studies may help to understand this relationship. Consequently, FMS patients should be examined for both physical and psychiatric symptoms in detail. If necessary, they may receive a psychiatric treatment as well. Evaluation of depression, anxiety, alexithymia and somatic amplification of FMS patients can be beneficial to minimize disability and increase QOL.

Authors' Contribution

Study Conception: ÖŞ, OOD; Study Design: ÖŞ, EA, GŞ; Supervision: ÖŞ, RE, GŞ; Funding: RE, EA; Materials: RE, EA; Data Collection and/or Processing: EA; Statistical Analysis and/or Data Interpretation: ÖŞ, EA, OOD; Literature Review: EA, OOD, RE; Manuscript Preparation: EA, ÖŞ and Critical Review: ÖŞ, OOD, RE, GŞ.

Conflict of interest

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The European Research Journal 2022;8(1):111-117 Original Article

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The correlation between primary dysmenorrhea and oxidative stress markers in adolescents

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ABSTRACT

Objectives: Primary dysmenorrhea is the most common gynecological complaint in adolescent girls. Among many factors, oxidative stress (OS) is thought to be a potential factor in the etiology of primary dysmenorrhea. In this study, it is thought that the use of IMA, thiol, and disulfide levels as a diagnostic marker in primary dysmenorrhea and antioxidant interventions may play a role in the treatment of primary dysmenorrhea and may benefit the pathophysiological and treatment process of the disease.

Methods: Thirty adolescent girls (study group) with grade 2.3 primary dysmenorrhea who applied to outpatient clinic and 30 healthy young girls (control group) of similar age group were included in the study. Primary dysmenorrhea grade was analyzed with the help of the visual analog scale (VAS) and verbal multidimensional scoring system (VMS). Patient`s basal hormone levels in the early follicular phase, serum albumin, IMA, total thiol, native thiol, disulfide, C-reactive protein (CRP), and cancer antigen-125 (CA-125) were recorded as main parameters.

Results: Oxidative stress markers were compared between the primary dysmenorrhea and control groups. Although albumin, IMA, and disulfide levels were higher on average in the group with dysmenorrhea, the difference was not statistically significant. Disulfide level was found to be significantly higher in the group with CA125 ≥ 35.

Conclusions: In our study, we examined serum albumin, IMA, total thiol, native thiol and disulfide levels in two groups resuts were not statistically significant. In this study, we concluded that as the CA125 level increased, the disulfide level increased in parallel.

Keywords: Adolescents, dysmenorrhea, oxidative stress

Primary dysmenorrhea refers to recurrent and cramp-like pain in the lower abdomen that occurs during menstruation in the absence of a pelvic pathology. It is the most common gynecological complaint in adolescent girls [1]. Primary dysmenorrhea is more common in young women and women who have not given birth yet [2]. The management of the disease begins by ruling out a pelvic pathology. Dysmenorrhea accompanied by a pelvic pathology is called secondary dysmenorrhea. The most common cause is endometriosis. Although secondary dysmenorrhea is more common in women in the 4th or 5th decade of life, it may rarely occur in adolescence.

Primary dysmenorrhea is caused by the increased production of endometrial prostaglandins during menstruation. Due to increased prostaglandins, the basal

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tone and active pressure of the uterus and dysrhythmic contraction pattern increase. The decreased uterine blood flow due to uterine hypercontractility and increased sensitivity in peripheral nerves contribute to pain. It starts a few years after menarche, after the ovulatory cycles settle down, and although it is more common in young women, it can continue until the 40s. The prevalence in adolescents ranges from 60% to 93% [3]. The pain is colic and begins a few hours before or with menstruation. Symptoms may be accompanied by nausea, vomiting, diarrhea, back pain, and syncope attacks. Early menarche, long menstrual periods, smoking, and high BMI may increase the severity and duration of pain.

Although the cause of primary dysmenorrhea is not fully understood, endometrial prostaglandins are thought to be associated with primary dysmenorrhea. It has been shown that PGF2alpha and PGF2alpha/PGE2 ratios increase in patients with primary dysmenorrhea, especially in the endometrium [4]. Prostaglandins are thought to cause pain by stimulating myometrial contractions, reducing uterine blood flow and oxygenation. During menstruation, when the uterus rises from the basal contraction level of 10 mmHg to 150-180 mmHg, uterine ischemia develops, and the released anaerobic metabolites stimulate type C pain fibers and cause dysmenorrhea [5]. Treatment options for dysmenorrhea include NSAIDs, COCs, and non-pharmacological alternative treatment options (such as TENS, acupuncture, exercise, diet) [6].

Prostaglandins are released from the endometrium during menstruation, increasing intrauterine pressure, and uterine ischemia develops. Ischemia leads to proinflammatory reaction cascades that lead to reactive oxygen radical production. Oxidative stress (OS) is defined as an imbalance between free radicals that occur as a result of normal metabolism or pathologically in living organisms and the antioxidant defense system, which has a protective role against free radicals [7, 8]. OS is thought to cause diseases by creating toxic effects on carbohydrate, protein, lipid, and DNA metabolism. Among many factors, OS is thought to be a potential factor in the etiology of primary dysmenorrhea. In the presence of OS, normal human serum albumin (HSA) undergoes modification and turns into ischemia-modified albumin (IMA) form with reduced affinity for metals such as cobalt, nickel, and copper [9]. IMA is a metabolic variant resulting from ischemic conditions in serum albumin. Increased free levels of IMA are studied as a simple and new marker for OS, hypoxia, inflammation, and endothelial dysfunction in some endocrine disorders [10]. Dynamic thiol/disulfide homeostasis has also recently been identified as an oxidative stress marker and has been shown to contribute to antioxidant defense, detoxification, and apoptosis [11]. It is an organic component containing the thiol-SH group and is an important component of the antioxidant system. The primary target of reactive oxygen radicals (ROS) is -SH groups of sulfur-containing amino acids, and the first action of ROS is to convert -SH groups into reversible disulfide bonds by oxidation. Disulfide bonds can be reduced back to thiol groups, and in this way, thiol/disulfide homeostasis is achieved [12].

This study aimed to evaluate uterine ischemia occurring during dysmenorrhea with oxidative stress markers such as IMA, thiol/disulfide. In this study, it is thought that the use of IMA, thiol, and disulfide levels as a diagnostic marker in primary dysmenorrhea and antioxidant interventions may play a role in the treatment of primary dysmenorrhea and may benefit the pathophysiological and treatment process of the disease.

METHODS

Patient Selection and Study Protocol

Thirty adolescent girls (study group) with grade 2.3 primary dysmenorrhea who applied to the University of Health Sciences Zekai Tahir Burak Health Application and Research Center youth center polyclinic between April 2019 and August 2019, and 30 healthy young girls (control group) of similar age group, who did not have any additional disease and did not have primary dysmenorrhea, were included in the study. Those with endocrinological (adrenal hyperandrogenism, Cushing's syndrome, DM) and chronic disease and those who used drugs were excluded from the study.

All patients underwent general physical and pelvic examination, detailed anamnesis was obtained, and sociodemographic characteristics were recorded. Primary dysmenorrhea grade was analyzed with the help of the visual analog scale (VAS) and verbal multidi-

mensional scoring system (VMS). Patients' age, body mass index (BMI), waist circumference, hip circumference measurements, waist/hip ratios, age at menarche, menstrual patterns, basal hormone levels in the early follicular phase, serum albumin, IMA, total thiol, native thiol, disulfide, C-reactive protein (CRP), and cancer antigen-125 (CA-125) were recorded as main parameters. The ovarian and uterus imaging of the patients was performed by abdominal ultrasonography. Blood samples were taken from the antecubital vein (approximately 10 ml) on the morning of the 2nd or 3rd day of menstruation for basal hormone levels and after 8 hours of night fasting for the evaluation of biochemical parameters, and the samples were taken to the laboratory within 10 minutes.

Thiol and disulfide and IMA levels were analyzed by a newly developed method by Erel and Kosem [11]. In summary, the reducible disulfide linkages were reduced to free functional thiol groups. Half of the difference between total and native thiol provides the dynamic disulfide amount. After determining the amount of native thiol and disulfide, the ratio of native thiol/disulfide was measured. Measurement analyses were performed blindly to the clinical information and course of the patients, and results were not available to the treating clinician, study group, or researchers during the study period.

Ethical approval was obtained (Date: 16.01.2019, Decision No:11/2019) from Dr. Zekai Tahir Burak Education and Research Hospital and the study was conducted in accordance with the Helsinki Declaration.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 23 program was used in the data analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standart deviations for normally distributed variables. Parametric methods were used in the analysis of normally distributed variables. The independent samples T-test was used in the comparison of two independent groups. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

The study was conducted between April 2019 and August 2019 on a total of 60 patients aged between 15-22 years. Albumin, IMA, thiol, and disulfide levels were compared between the primary dysmenorrhea and control groups. Although albumin, IMA, and disulfide levels were higher on average in the group with dysmenorrhea, the difference was not statistically significant ($p > 0.05$). Although native thiol and total thiol levels were lower on average in the group with dysmenorrhea, the difference was not statistically significant ($p > 0.05$) (Table 1).

Anthropometric characteristics of the cases are shown. Of the 60 cases, 30 had primary dysmenorrhea, and 30 were healthy individuals who applied to the youth center polyclinic. The mean age of the dysmenorrhea patients was 19.63 ± 2.93 years, and the mean age of the control group was 18.33 ± 2.56 years, and there was no statistical difference. Body mass index,

Table 1. Comparison of oxidative stress markers between the groups

	Dysmenorrhea group (n = 30) Mean ± SD	Control group (n = 30) Mean ± SD	*p* value
Albumin	4.29 ± 0.09	4.26 ± 0.1	0.211
Albumin adjusted IMA	0.98 ± 0.2	0.96 ± 0.21	0.777
IMA	0.98 ± 0.2	0.97 ± 0.2	0.858
Native Thiol	409.52 ± 26.14	414.99 ± 29.49	0.450
Total Thiol	449.67 ± 29.13	459.1 ± 32.3	0.240
Disulphide	22.32 ± 3.45	21.0± 2.64	0.108

IMA = ischemia-modified albumin

Tablo 2. Anthropometric characteristics of dysmenorrhea and control cases

	Dysmenorrhea group (n = 30) Mean ± SD	Control group (n = 30) Mean ± SD	*p* value
Age (years)	19.63 ± 2.93	18.33 ± 2.56	0.073
BMI (kg/m^2)	21.28 ± 2.75	21.21 ± 3.40	0.937
Waistline (cm)	70.20 ± 7.99	70.10 ± 9.85	0.966
Hip circumference (cm)	96.30 ± 6.96	95. 20 ± 7.55	0.560
Hip/waist ratio	0.72 ± 0.04	0.73 ± 0.05	0.832

BMI = body mass index

waist circumference, hip circumference, and waist/hip ratios were similar between the two groups ($p > 0.05$) (Table 2).

When OS markers were compared in the smoker and non-smoker groups, statistically similar values were measured ($p > 0.05$). Smoking did not cause any change in the level of OS markers (Table 3).

When OS markers were compared according to the CA-125 level, disulfide level was found to be significantly higher in the group with CA125 ≥ 35 ($p < 0.05$). Other OS markers were found to be similar between the groups (Table 4).

OS markers were compared between patients with a primary dysmenorrhea severity of VMS grade 2 and

Tablo 3. Comparison of OS markers in smoker and non-smoker groups

	Smoker (n = 6) Mean ± SD	Non-smoker (n = 54) Mean ± SD	*p* value
Albumin	4.24 ± 0.14	4.28 ± 0.08	0.357
Albumin adjusted IMA	0.87 ± 0.05	0.98 ± 0.21	0.212
IMA	0.88 ± 0.06	0.98 ± 0.20	0.239
Native thiol	397.31 ± 31.40	413.91± 27.15	0.167
Total thiol	437.70 ± 32.06	456.24 ± 30.47	0.165
Disulphide	21.64 ± 3.13	21.67 ± 3.14	0.688

IMA = ischemia-modified albümin, OS = oxidative stress

Table 4. Comparison of OS markers according to the CA-125 level

	CA125 < 35 Mean ± SD	CA 125 ≥ 35 Mean ± SD	*p* value
Albumin	4.27 ± 0.09	4.31 ± 0.09	0.241
Albumin adjusted IMA	0.96 ± 0.20	1.02 ± 0.17	0.441
IMA	0.96 ± 0.20	1.02 ± 0.17	0.513
Native thiol	413.55 ± 28.10	402.41± 24.65	0.323
Total thiol	454.64± 31.51	452.40± 27.53	0.858
Disulphide	21.35 ± 3.00	24.12 ± 3.06	**0.026**

IMA = ischemia-modified albümin, OS = oxidative stress, CA 125 = cancer antigen 125

Table 5. Evaluation of OS markers according to the VMS score

	VMS Grade 2 Mean ± SD	VMS Grade 3 Mean ± SD	*p* value
Albumin	4.29 ± 0.09	4.28 ± 0.90	0.648
Albumin adjusted IMA	0.99 ± 0.21	0.93 ± 0.16	0.515
IMA	0.99 ± 0.21	0.94 ± 0.16	0.554
Native thiol	411.26 ± 26.74	405.45 ± 25.74	0.586
Total thiol	449.32 ± 28.41	450.47 ± 32.51	0.923
Disulphide	22.25 ± 2.14	22.47 ± 5.62	0.873

IMA = ischemia-modified albümin, OS = oxidative stress, VMS = verbal multidimensional scoring system

grade 3. As the severity of dysmenorrhea increased, the level of OS markers did not change statistically (Table 5).

DISCUSSION

Although OS is associated with primary dysmenorrhea, studies on the subject are limited. The end products of OS and associated metabolites have become targets in therapeutic approaches for diseases associated with intense inflammation and endothelial dysfunction [13].

The menstruation of the participants aged between 15 and 22 and included in the study was regular, the mean age at menarche was 12 in both groups, the mean length of menstruation period was 5.8 days in the dysmenorrhea group and 6.2 days in the control group. Although serum albumin, IMA, and disulfide levels were higher on average in the group with dysmenorrhea, the difference was not statistically significant. Although the native thiol and total thiol levels were lower on average in the group with dysmenorrhea, the difference was not statistically significant. There is no other study in the literature evaluating these markers, which are indicators of oxidative stress in patients with primary dysmenorrhea. Therefore, our study is the first one in this regard. However, there are other studies in the literature stating that OS markers increase in primary dysmenorrhea. For example, in a study examining lipid and protein peroxidation markers among university students with dysmenorrhea in Nigeria, malondialdehyde (MDA) values were significantly higher in the group with dysmenorrhea [14]. This study also supports the studies conducted by Turhan *et al*. [15] and Dikensoy *et al*. [16]. This study carried out on Nigerian women also determined higher plasma nitrotyrosine (3-NT) levels and lower plasma alpha tocopherol (vitamin E) levels in the dysmenorrhea group. Protein carbonyls (PrCarb) levels did not differ between the groups [14]. While Turhan *et al*. [15], in their study investigating the oxidative stress balance in patients with primary dysmenorrhea using multiple serum markers, found the malondialdehyde (MDA) level to be high in the dysmenorrhea group as stated above, they found nitrotyrosine (3-NT), deoxyguanosine (8-OHdG) and superoxide dismutase (SOD) levels to be similar between the groups. They also detectedno correlation between the level of oxidative stress markers and the severity of dysmenorrhea [15]. In the study performed by Dikensoy *et al*. [16], malondialdehyde (MDA), nitric oxide (NO), and adrenomedullin (AM) levels were found to be significantly higher in the dysmenorrhea group. They concluded that lipid peroxidation and oxidative stress played an important role in the etiopathogenesis of primary dysmenorrhea [16].

When the anthropometric characteristics of dysmenorrhea and control cases were compared, the mean BMI was 21%, the mean waist circumference was 70 cm, the waist/hip ratios were similar in both groups, and no difference was found between the groups. It was reported that menstruation in adolescents did not show a significant correlation with body mass index [17]. In a study investigating the factors affecting the severity of dysmenorrhea, it was concluded that height, weight, and menstrual cycle length were not associated with the severity of dysmenorrhea, but there was a strong correlation with age at menarche and smoking. It was determined that the prevalence of

dysmenorrhea was higher and the symptoms were more severe in smoking women [18, 19]. In our study, we could not determine a correlation between the severity of dysmenorrhea and smoking, as we did not detect a difference in the level of OS markers in the smoker and non-smoker group, in contrast to the findings in the above-mentioned study. At the same time, when we evaluated the severity of dysmenorrhea by grading with the VMS score, we found that the severity of dysmenorrhea and the levels of OS markers did not change. Furthermore, although albumin, IMA, and disulfide levels were higher in the group with CA 125 ≥ 35 than the group with low CA-125, the difference between only disulfide levels was statistically significant.

Limitations

The small number of patients included in the study (30 patients with dysmenorrhea, 30 controls) and the lack of quantitative diagnostic criteria to define dysmenorrhea are the weaknesses of our study and are likely to have affected our results. The place of the level of OS markers in the diagnosis of dysmenorrhea should be supported by studies involving larger patient groups and adult women of reproductive age.

CONCLUSION

Since primary dysmenorrhea is a gynecological problem experienced by many young women and significantly affects their quality of life, it is reasonable to investigate OS in the etiopathogenesis of primary dysmenorrhea. The idea of controlling painful menstruation by reducing OS is important in this sense. In our study, in which we examined serum albumin, IMA, total thiol, native thiol, and disulfide levels in 30 women with dysmenorrhea and 30 healthy adolescents and young adults, changes were determined in the level of OS markers in the dysmenorrhea group compared to the control group, which was consistent with the literature, but not statistically significant. In this study, we concluded that as the CA125 level increased, the disulfide level increased in parallel. There is no other study on dysmenorrhea patients in the literature that investigates the OS markers we studied.

Authors' Contribution

Study Conception: BLK; Study Design: BLK; Supervision: BLK; Funding: BLK; Data Collection and/or Processing: BLK; Statistical Analysis and/or Data Interpretation: BT; Literature Review: BT; Manuscript Preparation: BLK and Critical Review: BT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(1):118-121 Original Article

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Relationship of thyroid gland elasticity with age, gender and thyroid gland volume in the shear-wave ultrasound elastography

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ABSTRACT

Objectives: The aim of the study is to determine the correlation between thyroid gland elasticity with thyroxine, thyroid-stimulating hormone levels, age, gender and thyroid gland volume in the normal population.

Methods: The study was conducted with 105 healthy cases. Thyroid gland elasticity was evaluated in axial plan using ultrasonography.

Results: The relationship between thyroid gland elasticity and thyroxine, thyroid-stimulating hormone levels, age, gender and thyroid gland volume was evaluated. The mean thyroid gland volume was 11.95 ± 9.23 mm3. A moderate negative correlation was found between thyroid gland volume and kPa value observed from the elastography examination. A moderate negative correlation was found between elastography kPa value and blood thyroxine level. No correlations were found between thyroid-stimulating hormone level, age, gender and thyroid gland elasticity.

Conclusions: The negative correlation between thyroid gland volume and thyroxine level with thyroid gland elasticity should be considered in elastographic evaluations.

Keywords: Ultrasonography, elastography, thyroid, volume

Shear-wave ultrasound elastography (SWE) is a quantitative method used to measure the stiffness of tissues [1]. SWE applies vibration on tissues with a focused ultrasound pulse produced by the ultrasound transducer. The rate of vibration spreading within the tissue increases in parallel with the increase in the stiffness of the tissues [2]. SWE is often used to evaluate diffuse thyroid diseases and thyroid nodules [3]. The risk of malignancy increases as the stiffness in the thyroid nodules increases [3-5]. Thyroid gland elasticity also increases in thyroid gland inflammation [1].

The aim of the study is to determine the correlation between the thyroid gland elasticity in cases with normal thyroid function tests and no thyroid pathology, with thyroxine (T4), thyroid-stimulating hormone (TSH) levels, age, gender and thyroid volume with SWE.

METHODS

The study included 105 healthy individuals. Inclu-

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sion criteria were healthy individuals who had normal thyroid functions tests within the last two weeks. Exclusion criteria were as follows: 1) TSH or T4 levels anomaly; 2) Thyroiditis history; 3) Use of drugs affecting thyroid hormones; 4) History of thyroid operation; 5) Nodule in thyroid gland; 6) Radiotherapy of neck for any reason; 7) History of radioactive iodine use; 8) Thyroid hemiagenesis or ectopic thyroid tissue. This prospective study was approved by the institutional review board of the Ethical Committee of our hospital. Written informed consent was obtained from all parents.

SWE Measurement

Two radiologists examined all the patients by SWE. They were blinded to each other's examinations. The US elastography evaluations were performed using a US system (Acuson S3000; Siemens Medical Solutions, Mountain View, CA) with a linear transducer that enabled scanning with a frequency ranging from 4 to 9 MHz.

Thyroid gland was evaluated in supine position with B-mod US. Thyroid gland volume was calculated. Then, thyroid gland elasticity was evaluated in supine position. The Tissue elasticity was measured by Virtual Touch tissue quantification software quantitatively (Siemens Medical Solutions). The examination was repeated until high-quality data were collected with color coded quality maps. The high-quality data were frozen and saved. The region of interest (ROI) of the system was set to include the muscle. A rectangular electronic box-shaped region of interest of 5×5 mm was used for SWE measurements. Additionally, an SWE scale of 0-10 m/s was chosen. All measurements were repeated for 10 times in the largest area of the thyroid gland in the axial plan (Fig. 1). The mean of 10 measurements was automatically determined.

Statistical Analysis

The statistical analysis was conducted with SPSS software (version 21.0; IBM Corporation, Armonk, NY). The descriptive statistics in the study were given as mean and standard deviation. All data showed normal distribution with the Kolmogorov-Smirnov test. The correlation between thyroid gland and kPa-Vms values observed in the elastographic examination and gland volume, blood T4-TSH values and cases were analyzed with Pearson correlation coefficient test analysis. The correlation coefficients were regarded as perfect when $r \geq 0.91$, as good when $0.90 \geq r \geq 0.71$, as moderate when $0.70 \geq r \geq 0.51$, as weak when $0.50 \geq r \geq 0.31$ and nonexistence when $r \leq 0.3$. The statistical significance level was $p < .05$.

RESULTS

The ages of the persons changed between 22 and 61 years (mean; 44.71 ± 10.23 years). Of these per-

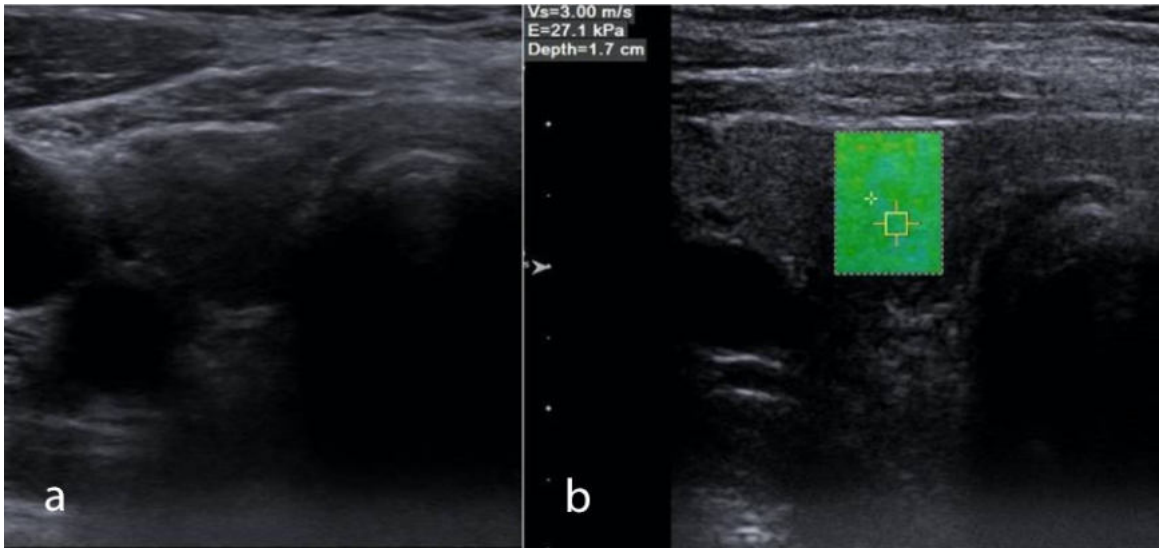

Fig. 1. (A) On B mod ultrasonography, the largest area in the thyroid right lob in axial plan, (B) Measurement made with SWE in the largest region in the axial plan.

Table 1. Descriptive analysis of the cases included in the study

	Mean ± Standard Deviation	Min.-Max.
Age (years)	44.71 ± 10.23	22-61
Thyroid gland total volume (mm^3)	11.95 ± 9.23	5-44.75
Thyroid gland elasticity (kPa)	13.01 ± 5.21	3.7-21.5
T4 level (ng/dL)	0.87 ± 0.17	0.61-1.15
TSH (mU/mL)	1.86 ± 1.22	0.78-4.60

T4 = thyroxine, TSH = thyroid-stimulating hormone

sons, 52 were males (mean age, 42.8 years; age range, 20-55 years), and 53 were females (mean age, 46.1 years; age range, 22-61 years).The mean thyroid gland volume was 11.95 ± 9.23 mm3. The descriptive data in the study were shown in Table 1.

A moderate negative correlation was found between thyroid gland volume and kPa value that was observed from the elastographic examination. A moderate negative correlation was found between elastography kPa value and blood T4 level while a weak positive correlation was found between elastography and blood TSH level. A weak negative correlation was found between age and kPa value. No correlations were found between gender and kPa value (Table 2).

DISCUSSION

Thyroid gland pathologies in adult patients and SWE examination results were evaluated in various studies [5-8]. The SWE value of the normal thyroid gland was evaluated in the limited number of studies [9-11].

The aim of the study was to determine the correlation between the thyroid gland elasticity with TSH, T4 levels, age, gender and thyroid gland volume in normal population, with SWE.

Arda *et al*. [7] was found 10.97 ± 3.1 kPa (range, 1-24 kPa) of the mean thyroid gland elasticity in the normal population [9]. The thyroid gland elasticity was found to be higher among women in this study. No correlations were found with age [9]. The mean thyroid gland elasticity value was 13.01 ± 5.21 in the present study. Unlike the study by Arda *et al*. [7], no significant differences were found with respect to gender in terms of thyroid gland elasticity. The correlation with thyroid volume and T4 was also evaluated in the present study unlike the study by Arda *et al*. [7]. A moderate negative correlation was found between elasticity and thyroid volume and T4 value in the study.

In a study conducted by Herman *et al*. [11] the elasticity of the neck anatomical structures in the normal population was evaluated and the mean thyroid gland elasticity was found as 9.5 ± 3.6 kPa. However, incidental thyroid nodules were detected in their study [11]. The cases with incidental nodules were excluded from our study.

It was found that thyroid gland elasticity is correlated with age, weight and height in the study by Habibi *et al*. conducted with normal children [10].Similarly, Uysal *et al*. [12], who conducted a study with children found a correlation with age. No correlations were found with age among adult cases in our study.

Sedlackova *et al*. [8], who conducted a study on diffuse thyroid diseases found a correlation between thyroid volume and stiffness similar to the present

Table 2. Pearson correlation test analysis between the elastography parameter of the cases and thyroid gland volume, blood T4-TSH levels, age, gender

	Thyroid Gland Volume		TSH		T4		Age		Gender	
kPa	k:-0.680**	***p* < 0.001**	k: 0.468*	***p* < 0.001**	k: 0.636**	***p* < 0.001**	k:-0.499*	***p* < 0.001**	k: 0.107	*p* = 0.276

study. No evaluation was performed in terms of age, gender, T4 and TSH levels in the study by Sedlackova *et al*. [8]. Previously, correlations were found between inflammation level and sclerosis with stiffness in diffuse thyroid diseases in [5].

Limitations

The main limitation in this study is that thyroid gland pathological evaluation was not conducted. Another limitation is the number of cases.

CONCLUSION

In conclusion, we used SWE to determine the elasticity values of various normal thyroid gland. Thyroid gland elasticity was not affected by age, gender, and TSH level. A moderate negative correlation was found between thyroid gland volume and T4 level with thyroid gland elasticity. Normal thyroid gland elasticity value can be used as a base value in the future studies. Additionally, the negative correlation between thyroid gland volume and T4 level with elasticity should be considered in elastographic evaluations.

Authors' Contribution

Study Conception: FEU, STU, SE; Study Design: FEU, BÖ, MK; Supervision: MK, STU; Funding: FEU, BÖ, SE; Materials: SE, BÖ, STU; Data Collection and/or Processing: FEU, SE, MK; Statistical Analysis and/or Data Interpretation: FEU, SE, STU; Literature Review: FEU, BÖ, MK; Manuscript Preparation: FEU, STU and Critical Review: MK, STU, BÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2022;8(1):122-125 Case Report

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COVID-19 pansinusitis with abducens paralysis

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ABSTRACT

Increasing numbers of the papers indicate that SARS-CoV-2 also causes neurological symptoms; the underlying mechanism has not been elucidated yet. Hypothetic mechanisms to explain the CNS involvement of SARS-CoV-2 include the neurotropic mechanisms and the cytokine storm developing during the disease process. A middle age female patient applied to the emergency department with complaints of eye pain, a double, foggy, and blurred vision and a severe throbbing headache. The outward gaze was found to be limited in her right eye. Nasopharyngeal swab for SARS-CoV-2 RNA was positive, radiological findings were supported the COVID pneumonia and diffuse sinonasal inflammation. Cranial imaging showed thickening and contrast involvement in the cavernous sinus in the postcontrast series. While shortness of breath improved, and the headache was completely resolved on the 10th day of treatment the right eye outward gaze restriction was continued. The control MRI reveals a significant reduction in cavernous thickening and contrast enhancement and complete resolution in dural thickening. In our case of COVID, cranial nerve involvement and pansinusitis developed without cytokine storm findings suggests that the virus has spread to the cavernous sinuses and dura by regional neighborhood. Neurological symptoms may appear as the first symptom of COVID.

Keywords: COVID-19, pansinusitis, abducens paralysis, headache

Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV-1) viruses have been shown to cause brain damage. Although increasing numbers of the papers indicate that SARS-CoV-2 also causes neurological symptoms, the underlying mechanism has not been elucidated yet. Hypothetic mechanisms to explain the CNS involvement of SARS-CoV-2 include the neurotropic mechanisms and the cytokine storm developing during the disease process [1]. The passage of the virus into the brain tissue can be by crossing the blood brain barrier(BBB) or by transsynaptic passage from infected neurons through the olfactory nerve [1]. SARS-CoV-2 has 10 to 20 times more affinity to ACE2 than SARS-CoV-1. Systemic inflammation that develops during the course of COVID-19 infection probably increases the permeability of BBB, allows infected immune cells, cytokines, and possibly the virus itself to pass to CNS [2].

In this report, we shared a COVID-19 case with the 6th cranial nerve palsy accompanied by pansinusitis in which neurological symptoms were the initial findings.

CASE PRESENTATION

A 60-years-old female with no prior history of chronic disease and drug use, applied to the emer-

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gency department with the complaints of ocular pain, double, foggy and blurred vision which had started after severe throbbing headache. She also had nausea, postnasal drip, accompanying mucus sputum, anosmia and ageusia. She was hospitalized and hydroxychloroquine (2×200 mg), azithromycin (500 mg 1×1), and low molecular weight heparin (Enoxaparin 6000 anti-Xa IU/0.6 ml 1×1) treatment were started upon detecting the findings supporting the COVID pneumonia (Fig. 1. A1 and A2) on the thorax computed tomography (CT). Severe loss of ventilation and diffuse sinonasal inflammation was observed in the paranasal sinus CT (Fig. 1B).

Her nasopharyngeal swab for SARS-CoV-2-RNA was positive. Green and foul-smelling diarrhea was added to her complaints on the 5th day of hospitalization. No fever observed. She was conscious, cooperated and orientated. Her visual acuity allows her to count fingers from 6 meters with both eyes. There were full muscle strenght on both upper and lower extremities, deep tendon reflexes were normoactive, sensory, and cerebellar tests were within normal limits. Muscle strength fluctuations was not observed during the follow-up. There was no ataxia and the Romberg test was negative. Fundus examination was normal and there was no evidence of papillary edema. The outward gaze was found to be limited in her right eye.

Magnetic resonance imaging (MRI) of the brain showed widespread contrast inflammation in the paranasal sinuses, as well as thickening and contrast involvement in the cavernous sinus in the postcontrast series. Diffuse thickening was observed in the posterior parietal and occipital wall (Fig. 1C and 1D). No sign of venous sinus thrombosis was observed.

The cerebrospinal fluid (CSF) examination revealed an opening pressure of 11 cmH2O (reference values 7-20 cmH2O), protein = 26.75 mg/dL (reference values: 15-45 mg/dL), glucose = 59 mg/dL (reference values: 40-70 mg/dL) with normal cytology. The bacterial culture, serological tests, routine blood tests and SARS-CoV-2 PCR of CSF was negative. Antibiotics and Favipiravir treatment was added to for-

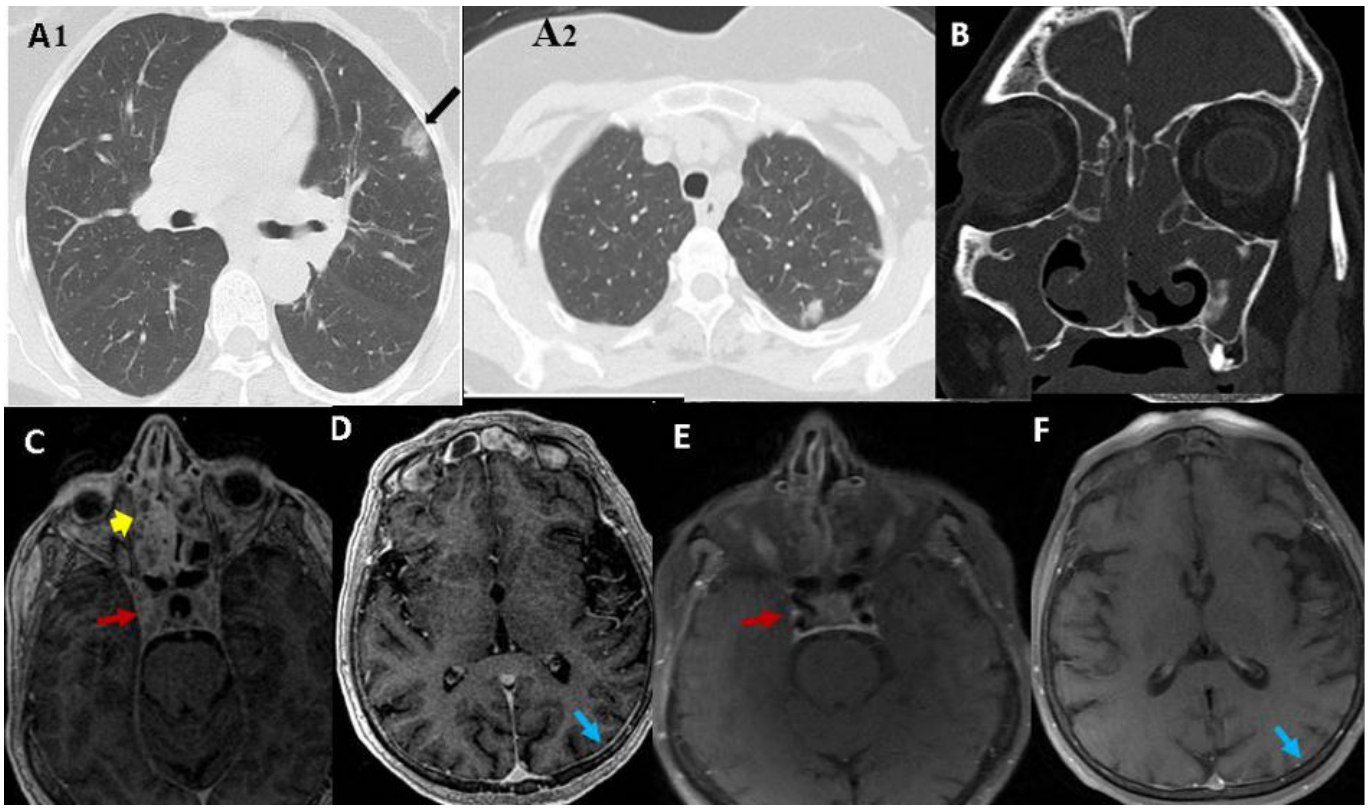

Fig. 1. (A1 and A2) = Parenchymal infiltration area (black arrow) in the left lung, upper lobe anterior-lateral, ground-glass density. (B) = Widespread inflammation and loss of aeration in the paranasal sinuses. (C-D) = Cavernosal thickening (red arrow) and sinonasal inflammation (yellow arrow) and diffuse thickening in the posterior parietal wall (blue arrow) in the postcontrast MR before treatment. (E-F) = Decline in cavernosal (red arrow) and dural thickening (blue arrow) in postcontrast MR after treatment.

mer treatment. Except right outward gaze restriction, headache was completely resolved, and shortness of breath improved on the 10th day of treatment. Cavernous thickening and contrast enhancement were significantly reduced, and dural thickening was completely resolved in the control cranial MRI (Fig. 1E and 1F).

DISCUSSION

The smell and taste disturbances commonly described in the course of various viral infections. These symptoms are reported to be seen independently of respiratory signs and symptoms during the COVID-19 disease process. Although these symptoms are not specific for COVID-19 they suggest olfactory bulb involvement, which is thought to be a way for the viruses to enter into the central nervous system [3]. In animal models, it has been shown that SARS-CoV-1, and MERS-CoV can enter to the brain through the olfactory nerves and then spread rapidly to certain brain regions [2]. In our case of COVID-19, cranial nerve involvement and pansinusitis developed without cytokine storm findings suggesting that the virus has spread to the cavernous sinuses and dura by local transmission. Marc Dinkin *et al*. [4] reported a case of abducens nerve involvement without radiological evidence and stated that an increase in the optic nerve sheath of the included eye may reflect viral leptomeningeal invasion. In our case, the fact that anosmia and ageusia are among the findings accompanying pansinusitis, as well as the presence of contrast enhancement on the side where there is abducens paralysis radiologically, seems to support this theory.

Myasthenia gravis, Guillain-Barre and Miller-Misher syndromes should be considered in differential diagnosis. Cranial nerve involvement is mostly associated with Guillain-Barre or Miller-Fisher syndromes which thought a parainfectious or postinfectious conditions [5]. Anamnesis and physical examination findings during the follow-up did not suggest these diagnoses. Unlike the others, neurological findings such as severe headache and cranial nerve involvement were observed as symptoms of presentation in our case. Response to the treatment was objectively documented with detailed neurological examination and cranial MRI results before and after treatment.

CONCLUSION

Neurological symptoms may appear as the first symptom of COVID-19. Detailed neurological examination, CSF analysis, and MRI are very important in depicting the course and spread of the disease. The neuroinvasive and neurotropic features of the SARS-CoV-2 virus may have neuropathological effects under unpredictable environmental and background genetic factors. This is a case report with evidence supporting the neuroinvasion of SARS-CoV-2 to the brain.

Authors' Contribution

Study Conception: MS, NK, YÇ, BH; Study Design: MS, NK Supervision: MS, NK; Funding: N/A; Materials: N/A; Data Collection and/or Processing: MS, YÇ; Statistical Analysis and/or Data Interpretation: MS, NK, YÇ, BH; Literature Review: MS, NK; Manuscript Preparation: MS, NK and Critical Review: MS, NK, BH.

Ethical statement

The case report was written with the guidance of CARE guideline

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Informed consent

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

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The European Research Journal 2022;8(1):126-130 Case Report

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Massive bilateral adrenal mass with adrenal insufficiency: a case report of primary adrenal lymphoma

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ABSTRACT

Primary Adrenal Lymphoma (PAL) is extremely rare and usually occurs in men in the 6th-7th decade as bilateral, diffuse large B-cell lymphoma (DLBCL). Here, an 80-year-old patient admitted to the urology outpatient clinic with flank pain and bilateral adrenal mass detected on ultrasound is presented. Positron Emission Tomography-Computed Tomography (PET-CT) was planned for the patient who was referred to the endocrine outpatient clinic. The PET-CT scan revealed lobulated-contoured masses containing necrotic areas with a size of 7.4×5.5×9.8 cm, 19 Hounsfield Unit (HU), and SUVmax value of 23.9 the right adrenal, and with the size of 8.4×8.7×10.8 cm, 28 HU, SUVmax value of 27.3 in the left adrenal. These masses were reported to be not compatible with metastasis and suggested a tumor of the adrenal origin or bilateral adrenocortical carcinoma. In laboratory tests, since Adrenocorticotropic hormone level 291-592 pg/mL (high) and Cortisol level was 7.5-9.5 mcg/dL (low), bilateral adrenalectomy was performed considering adrenocortical cancer primarily. Diffuse large B cell lymphoma was determined as the result of the pathology. Postoperative hydrocortisone and fludrocortisone treatment was initiated for the patient immediately. The patient was transferred to the hematology inpatient clinic to receive Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone chemotherapy. In this case report, we aimed to emphasize that the differential diagnosis should be made well in massive bilateral adrenal masses. Although the diagnosis is challenging, clinicians should be alert in diagnosing lymphoma in bilateral, massive adrenal masses with adrenal insufficiency. Since this disease's prognosis is poor and aggressive, a histopathological diagnosis should be obtained, and treatment should be initiated as soon as possible.

Keywords: Adrenal insufficiency, non-Hodgkin's lymphoma, primary adrenal lymphoma

Although lymphomas generally consist of lymphoid tissue, less than 25% of cases are of extranodal origin. Primary Adrenal lymphoma (PAL) is extremely rarely seen as less than 1% of all cases. It is usually seen as bilateral and non-germinal centered diffuse large B-cell lymphoma (DLBCL) in males in the 6th and 7th decade [1]. Although the etiology remains unknown, the Epstein-Barr virus, genetic defects in P53 and C-kit, and immune system dysfunction are considered responsible [2].

Here, an 80-year-old patient admitted with a flank pain complaint was operated considering adrenal carcinoma in the pre-diagnosis and diagnosed with bilateral high-grade B-cell lymphoma as the result of pathology is presented.

CASE PRESENTATION

An 80-year-old female patient with no known co-

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morbidities applied with left flank pain, fatigue, and weakness to the urology outpatient clinic. The ultrasonography examination revealed heterogeneous hypoechoic lesions with the size of 81×37 mm in the right adrenal and 85×50 mm in the left adrenal, and the patient referred to the endocrine outpatient clinic. In the patient's physical examination evaluated in our clinic, her blood pressure was 90/60 mmHg, and her pulse was 95/min. The examinations of all systems were normal, and there was no organomegaly. No abnormalities were found in routine biochemistry and complete blood count tests. The hormonal test results of the patient are presented in Table 1. With a pre-diagnosis of adrenal insufficiency, a 250 mcg intravenous synacthen stimulation test was performed on the patient. The adrenal insufficiency diagnosis was made based on the cortisol levels (Table 2). The Magnetic Resonance Imaging (MRI) of the patient was reported as space-occupying lesions with a size of approximately 70×50 mm in the left adrenal region, approximately 58×36 mm in the right adrenal region, slightly hypointense in T1, slightly hyperintense in T2, and a slight signal loss in out phase sequences (Figs. 1 and 2). Positron Emission Tomography-Computed Tomography (PET-CT) was requested to examine malignancy due to the mass's size, the patient's age, and the clinical presentation. PET-CT resulted as masses in right adrenal with 7.4×5.5×9.8 cm size, 19 Hounsfield Unit (HU), SUV max: 23.9, and left adrenal lobulated contoured 8.4×8.7×10.8 cm in size, 28 HU, SUVmax: 27.3. Necrotic areas were noticeable in both masses. Bilateral adrenal masses were not compatible with metastasis and were reported as either tumors of the adrenal origin or bilateral adrenocortical carcinoma. An endocrine department consultation was requested in the preoperative period. Considering the bilateral adrenal carcinoma and primary adrenal insufficiency first, the patient was operated under steroid infusion and bilateral adrenalectomy was performed. No complications occurred during or after the operation. Postoperative hydrocortisone 15 mg/day and fludrocortisone 0.1 mg/day treatment was started due to primary adrenal insufficiency. The patient's pathology result was reported as "Neoplastic cells are antigenically positive with CD20, CD79a, mum1, bcl6, and PAX5, negative with CD3, CD5, CD10, Tdt, CyclinD1, MPO, and CD34. Ki-67 proliferation index is around 90%, and no loss with BCL-2. Morphological and immunohistochemical findings are consistent with diffuse large B cell lymphoma infiltration, germinal off-center". The patient was transferred to the hematology inpatient clinic. R-CHOP (Rituximab - Cyclophosphamide + Doxorubicin + Vincristine + Prednisolone) chemotherapy was initiated.

Table 1. Preoperative hormonal test results

	1st Result	2nd Result	Comment
ACTH (pg/mL)	291	592	High
Cortisol (mcg /dL)	7.5	9.5	Low
24-hour urine metanephrine (pg/mL)	38	-	Normal
Plasma metanephrine (pg/mL)	72	-	Normal
Aldosterone/Renin ratio (ng/dl/ ng/ml/h)	17/2: 8.5		Normal
LDH (IU/L)	354	-	Normal
DHESO4 (mcg/dL)	102	-	Normal

ACTH = Adrenocorticotropic hormone, LDH = Lactate dehydrogenase enzyme, DHESO4 = Dehydroepiandrosterone sulfate

Table 2. Cortisol levels after synacthen stimulation test

	0 min	30th min	60th min	90th min	Comment
Cortizol (mcg/dL)	7.5	8.0	8.5	9	Low

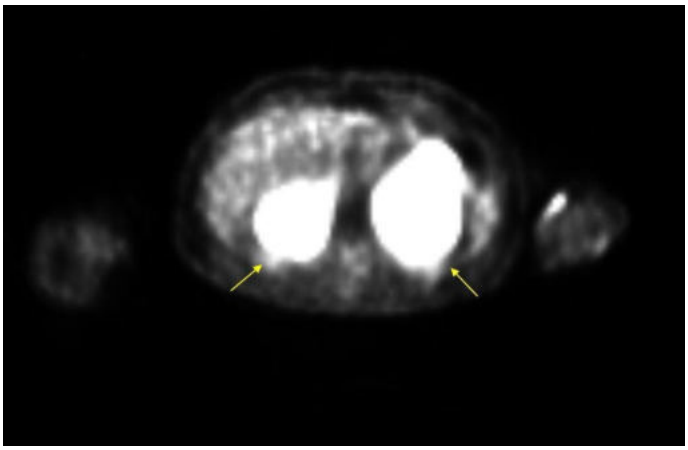

Fig.1. In diffusion-weighted images, mass lesions showing diffusion restriction are observed in the bilateral adrenal glands.

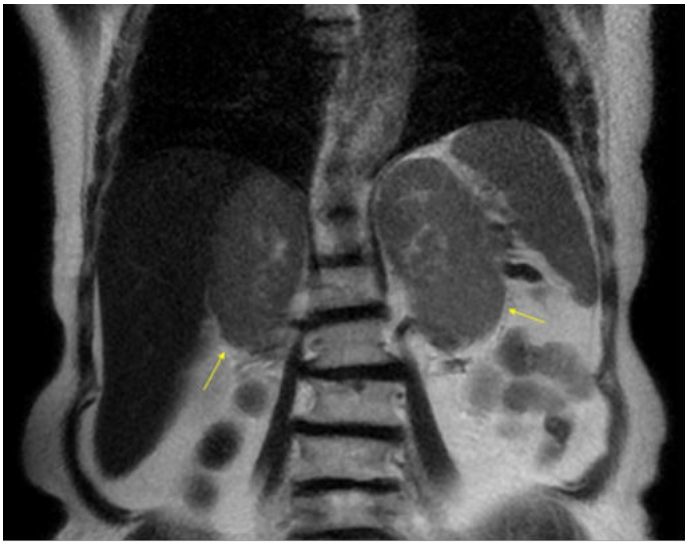

Fig. 2. Coronal T2-weighted images, hyperintense mass lesions of uniform character with smooth borders are observed in bilateral adrenal glands.

DISCUSSION

Adrenal masses are seen more frequently with the development of imaging methods.Bilateral adrenal masses constitute approximately 15% of the adrenal masses detected incidentally [3]. Granulomatous diseases, hemorrhage, metastatic lesions, or lymphoma should be suspected when bilateral, bulky masses are detected in the adrenal gland [4]. Bilateral primary adrenal .lymphoma (PAL) of the adrenal gland is very rare. Its diagnosis is challenging, the prognosis is aggressive, and there is no specific laboratory test to make a diagnosis. LDH may be found to increase at a rate of 88%, especially in patients with bilateral masses [2]. However, the LDH level was within the normal reference range in our patient. Just as there is no laboratory finding to diagnose PAL, there are no specific symptoms either. The patient can also present with nonspecific findings such as abdominal pain, weight loss, and adrenal insufficiency-related presentations such as hypotension, fever, fatigue, and hyperpigmentation. The adrenal cortical insufficiency occurs more often when 90% of the adrenal parenchyma is destructed in advanced primary disease stages [5]. Systemic symptoms such as fever, weight loss, and night sweating in malignancies are called B-symptoms, and they are generally seen more in patients with large bilateral masses than the unilateral and small ones. This phenomenon has been attributed to tumor burden and cytokine storm released from lymphoid cells [2]. However, although our patient had massive bilateral masses, there were no B-symptoms contrary to this information.

Radiographic features are beneficial in the differential diagnosis of adrenal masses. The most commonly used imaging methods are Computed tomography (CT) and MRI. Through its ease of access, low cost, and short examination time, CT becomes prominent as the first test to evaluate adrenal lesions. In unenhanced CT, the lesion being less than 10 HU, homogeneous, well-circumscribed, and small in diameter favors benign lesions, while as the size of the lesion increases, the likelihood of malignancy of the lesion increases as well. After excluding pheochromocytoma, 70% of the adrenal masses larger than 4 cm are malignant and this rate increases to 85% as the size increases over 6 cm [6]. Rapid loss of contrast (washout) in 10th-15th min post-contrast images in contrast-enhanced CT images is an essential indicator for detecting benign lesions. MRI and PET-CT are used in the differential diagnosis of adrenal lesions with low-fat content detected by CT. In adrenal lymphoma, there is no typical diagnostic image in imaging methods. In CT, nodular and diffuse thickening can be seen in the gland, imaging findings other than low density, low-moderate contrast overalls (no contrast washout and signal loss, diffusion restriction, and activity uptake) are that the hypointense pattern can be seen in T1 and hyperintense pattern in T2 in MRI; however, these findings are similar to other malignant diseases [7]. In our patient, there were no specific findings suggesting lymphoma on imaging. We predicted

it was a malignant mass since the imaging findings of adrenal carcinoma include the large size of the lesion, heterogeneous and distinct contrast enhancement, absence of contrast washout phenomenon, no signal loss in chemical shift imaging, diffusion restriction in diffusion-weighted imaging, and activity uptake in PET-CT images [8]. Based on the PET-CT findings, this patient was evaluated in favor of adrenal carcinoma and underwent adrenalectomy. Maybe a biopsy could be performed for this patient before the operation. However, the issue of biopsy in adrenal lesions is controversial. While some authors consider CT-guided biopsy as an easy and reliable method in cases with hesitation in diagnosis [8], some authors recommend biopsy only if it will change the course of oncological disease treatment with known malignancy. The sensitivity of adrenal biopsy performed with a pre-diagnosis of malignancy is 87%, and the specificity is 100% [9].

A biopsy was not performed in our case; the patient underwent adrenalectomy based on imaging methods, considering adrenal carcinoma in the pre-diagnosis. The diagnosis of the disease was made by pathological examination. There were no distant metastases in the CT taken for staging after the operation. Based on these findings, our patient was diagnosed with PAL. PAL prognosis is generally poor, rapidly progressing, and aggressive. Although it initially appears to respond well to treatment, permanent remission is rare [10]. The average 1-year survival is less than 20%, so it should be treated aggressively. There is no specific treatment regimen for PAL. Through CHOP and similar treatments with or without rituximab, survival is between 20-50%. There is no difference in survival in the disease being unilateral and bilateral, as well as no difference in terms of treatment between undergoing surgery (adrenalectomy) or only chemotherapy. Information on the effectiveness of radiotherapy is very limited, and larger studies are needed.

CONCLUSION

As a result, lymphoma associated with the adrenal gland is extremely rare and difficult to diagnose. First of all, the clinician should have a high degree of suspicion in patients with adrenal insufficiency and bilateral adrenal mass. The diagnosis is made by imaging-guided biopsy, surgical resection, or autopsy. Since its prognosis is poor, the diagnosis should be made quickly, and treatment should be started as soon as possible.

Authors' Contribution

Study Conception: SÇA; Study Design: SÇA; Supervision: SÇA; Funding: SÇA; Materials: SÇA; Data Collection and/or Processing: UA; Statistical Analysis and/or Data Interpretation: UA; Literature Review: SÇA; Manuscript Preparation: SÇA and Critical Review: SÇA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Informed consent

Written informed consent was obtained from the patient for publication of this case and any accompanying images.

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The European Research Journal 2022;8(1):131-138 Review

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Effects of microRNAs in hypertension disease

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ABSTRACT

Objectives: Hypertension is a cardiovascular disease which is a very common hemodynamic syndrome, and it has different prevalence in different regions as it is common all over the world. In recent studies, it is known that microRNAs (miRNAs) play an important role in hypertension disease and that miRNA expressions are regulated by epigenetic mechanisms. There are also studies proving that microRNAs are new therapeutic targets for pulmonary arterial hypertension, and miRNAs can participate in the pathophysiology of hypertension in many ways and it can be used as a biomarker for hypertension disease. It is thought that miRNAs can be effective in the diagnosis and treatment of hypertension and further studies are needed. Recently, the relationship between miRNAs and hypoxia has also been focused on and has been taken into account in studies. In this review, we aimed to present the effects of miRNAs on hypertensive disease and current approaches. Finally, with gene targeting studies, we think that miRNAs, which can be biomarkers and molecular agents, will hold promise in preventing the progression of hypertension in the future, and we hope that they can create ideas for future studies.

Keywords: miRNA, hypertension, epigenetic

Hypertension is a common cardiovascular disease that occurs with high blood pressure. Hypertension disease causes harmful complications and poses a risk for diseases such as stroke, coronary artery disease, heart failure and chronic kidney failure [1, 2]. In addition, hypertension (HTN) is a disease that continues to be quite common around the world. Essential hypertension (EH) is a highly complex and polygenic condition, and in addition epigenetic modifications are very important in the development of EH. Known for genetic and environmental systems involved in determining the risk of EH Genetic and environmental systems are known involved in determining the risk of EH (Fig. 1) [3].

Nitric oxide acts as an anti-inflammatory agent and prevents leukocyte adhesion. This prevents vascular inflammation and causes vasodilation, resulting in hypertension [4]. Pulmonary hypertension (PH) is a lung disease that occurs when the pulmonary artery pressure reaches a quarter of the blood pressure in the whole organism. Recent studies focus on the importance of microRNAs (miRNAs) and are underway in many recent studies on the effects of miRNAs in human disease [5]. miRNAs are non-coding RNAs of about 21-25 bp long and play an important role in various biological processes such as differentiation, proliferation, migration, and apoptosis on hypertension diseases as with all diseases (Fig. 2) [2, 5, 6, 7].

The formation of miRNA is based on the occurrence of a number of processes in the cell, nucleus and cytoplasm. The first miRNA synthesized is called pri-miRNA and is about 700 bases long. This primary miRNA is synthesized by RNA polymerase II. It has a cap (5 'cap) and a poly-A tail. After the pri-miRNA

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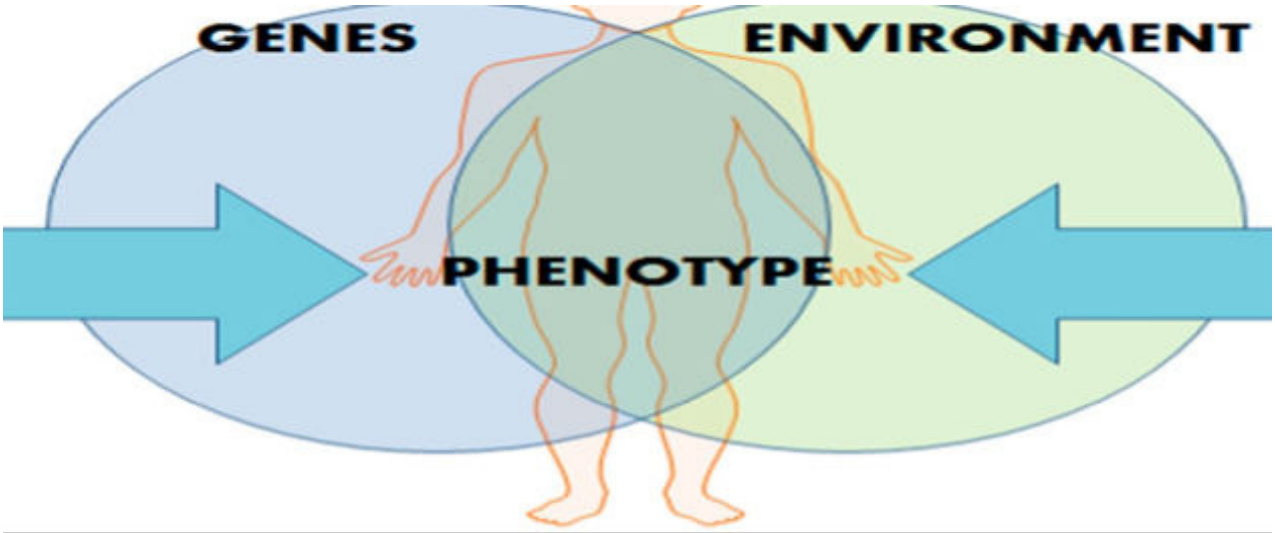

Fig. 1. Effects on phenotype. Genetic and environmental systems are effective in the development of essential hypertension [3].

is cleaved by the Dorsha enzyme, a precursor miRNA called pre-miRNA is formed and is about 70 bases long. The precursor miRNA is then transported through nuclear pores to the cytoplasm. This transport takes place with the exportin-5 protein. The stem ring of pre-miRNAs is then cut with the Dicer enzyme, resulting in two complementary short RNA molecules. The stable, i.e. mature miRNA binds to the RNA-derived silencing complex (RISC) and performs its function. Lost when other RNA is broken down (Fig. 3) [6, 8, 9].

Non-coding RNAs are divided into two; small non-coding RNAs and long non-coding RNAs. Long non-coding RNAs are regulated by miRNAs. In addition, the main functions of miRNAs include their role in gene regulation by binding to the RNA-ınduced silencing complex (RISC). In the regulatory complex that has formed, Argounate functions as the main protein. Small RNAs are found in the active site of the Argounate protein, miRNA and mRNA forms the triple complex. Causes a pressure on gene expression through mRNA cleavage or translational suppression (Fig. 4) [10, 11].

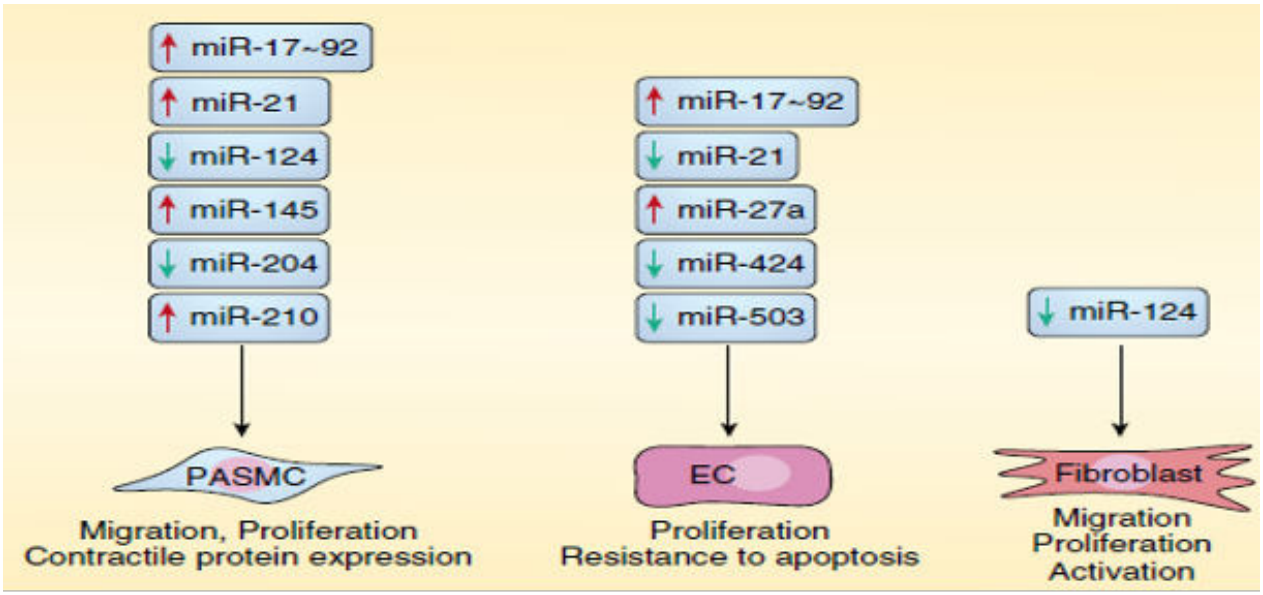

Fig. 2. Schematic diagram showing microRNAs contributing to the pathogenesis of pulmonary arterial hypertension [7]

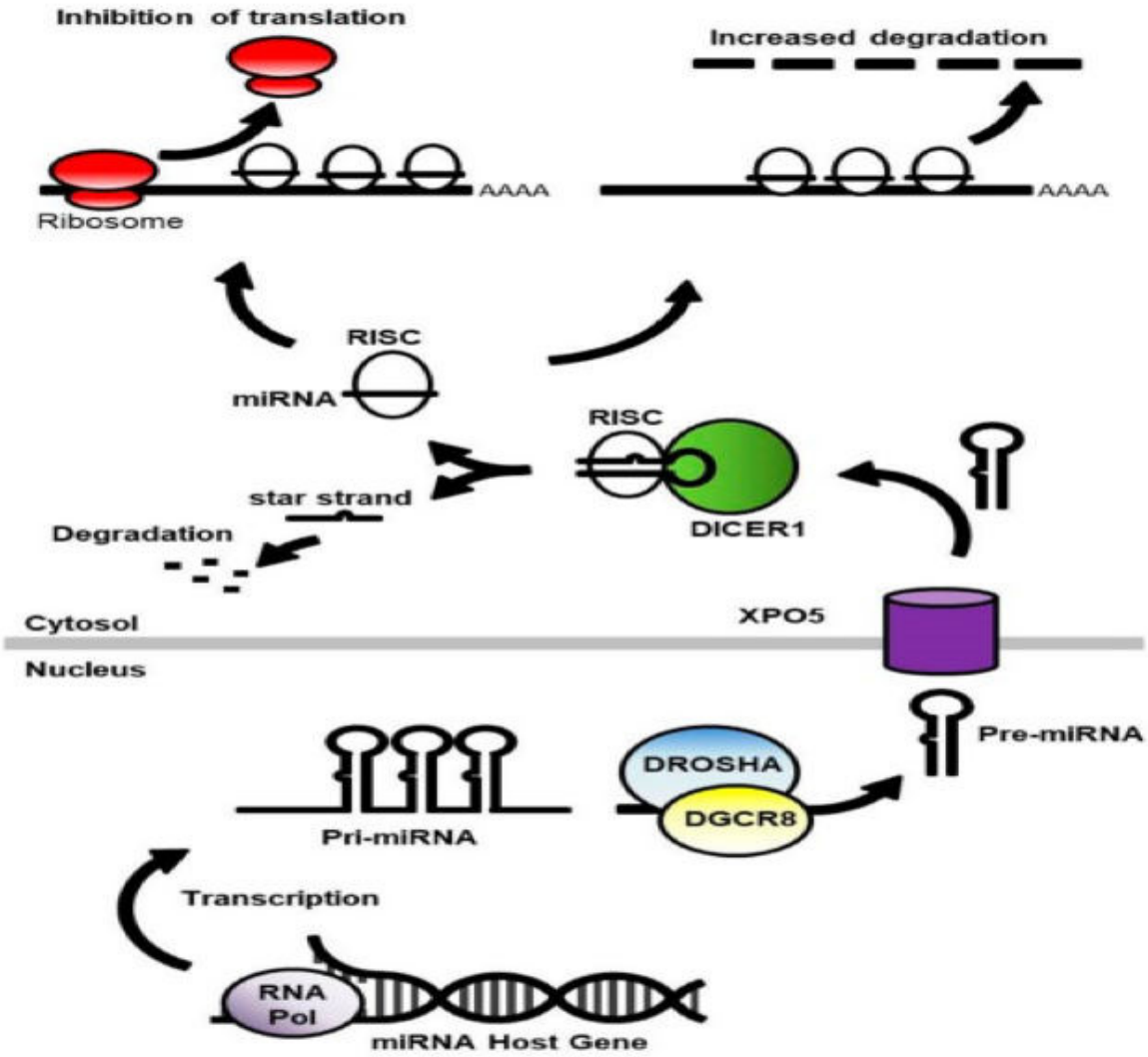

Fig. 3. Schematic view of microRNA (miRNA) processing and function [9].

Epigenetic Mechanisms and Its Effect on Hypertension Disease

miRNAs play an important role as epigenetic modulators by interacting with enzymes involved in epigenetic mechanisms such as DNA methyltransferase (DMTs), histone deacetylase (HDACs), and histone methyltransferases (EZHs). In addition, epigenetic mechanisms such as DNA methylation, RNA modification, and histone modification regulate the expression of miRNAs. With miRNAs, epigenetically related cell proliferation creates a new mechanism in regulating cell processes such as apoptosis and differentiation. Additionally, miRNAs can affect the expression of the epigenetic mechanism by targeting enzymes that are associated with epigenetics. MiRNAs are increasingly important in epigenetic expressions, such as; DNA methylation, RNA modification and histone modification (Fig. 5) [12, 13].

Epigenetic mechanisms play an important role in expressing the inherited characteristics that contribute to the pathogenesis of many cardiovascular diseases and in the transmission of risk factors for hypoxia-sensitive pulmonary arterial hypertension (PAH) from generation to generation (Fig. 6) [14, 15].

The Prevalence of Hypertension Disease in the World and in Turkey

There are important differences in the prevalence of HTN in the USA; Hypertension is seen in 43% of African American women, 45.7% of men, 33.9% of white men and 31.3% of women. In a healthy 45-year-old African American, the risk of developing HTN is 92.7%, compared with 92.4% in Hispanic populations. On the other hand, the risk of developing HTN among

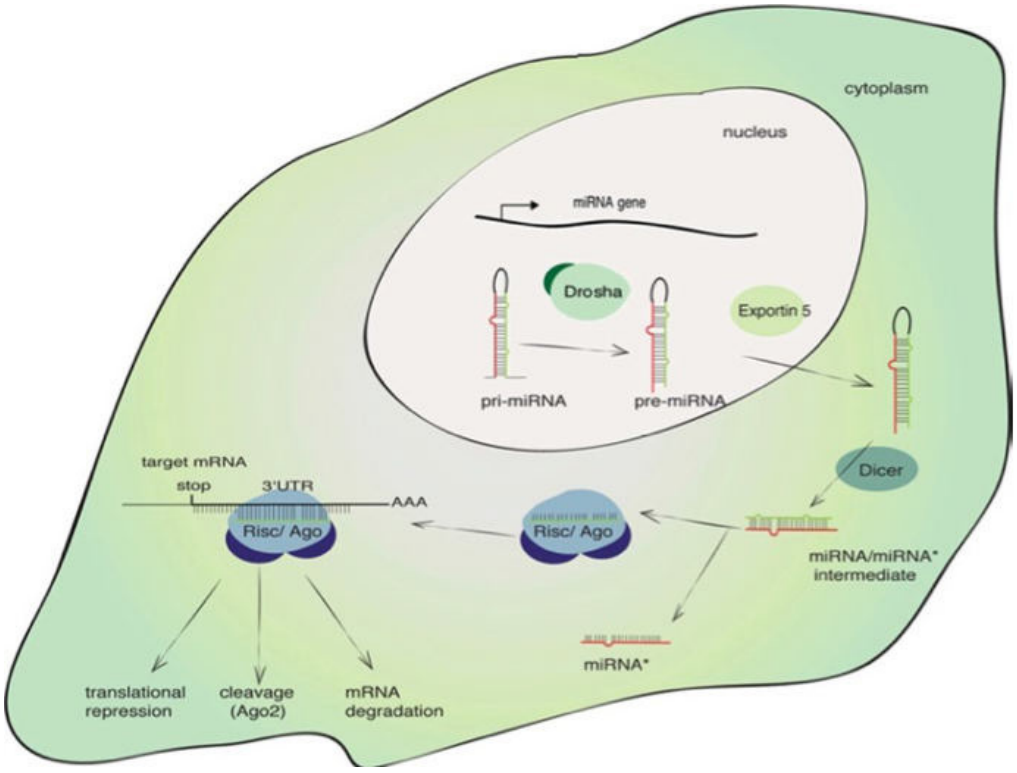

Fig. 4. Schematic overview of the miRNA pathway [10].

Caucasians is relatively low (up to 86%) and even lower in Asian populations (84.1%) [4]. Hypertension affects approximately 25% of the adult population worldwide, and it is estimated that the number of adults with hypertension will increase by approximately 60% in the coming years. In the United States, hypertension affected 30% of the population in 2015. According to the "2017 High Blood Pressure Clinical Practice Guidelines", the prevalence of hypertension has increased significantly (46 to 32%) among US adults [2]. Hypertension is a widespread public health problem in our country as well as all over the world. According to the "Turkish Hypertension Prevalence Study", the prevalence of hypertension in adults (18 years and older) is 31.8% (males; 27.5%, females; 36.1%). Blood pressure control in all hypertensives is 8%, and it is 20.7% in patients who are aware of high blood pressure and who are treated [16].

miRNAs Related to Hypertension Disease

According to studies conducted in hypertensive patients, a significant increase in miR-21 expression levels compared to healthy control group was observed. The mechanism of miR-21 increased in target organ damage is unknown. Moreover, miR-21 is a molecule involved in the regulation of vascular remodeling during EH [2]. In recent studies, it has been reported that with a decrease in miR-21 expression levels, it has a role in regulating the Programmed cell death protein 4 (PDCD4) and Activator protein 1 (AP-1) signaling pathway [17].

miRNAs are expressed differently in many diseases, including pulmonary hypertension (Fig. 2). One study reported that miR-204 is involved in reducing blood pressure [7, 18]. In one study, miR-214 was known to downregulate Phosphatase and tensin homolog (PTEN) and suppress apoptosis and promote the proliferation of Pulmonary Artery Smooth Muscle Cells (PASMCs). Thereupon, in the same study, it was found that miR-214 targets PTEN. As a result, miR-214 is thought to be a promising diagnostic tool for pulmonary hypertension (PH) [5]. Also In recent studies, it has been stated that miR-214 plays a role in controlling perivascular fibrosis [19].

In the studies conducted, it was observed that hsa-miR-145 expression increased significantly in atherosclerotic plaques taken from hypertensive patients compared to the health control group. It has been noted that hsa-miR-145 and hsa-miR-122 are associated with the development of hypertension. Also hsa-

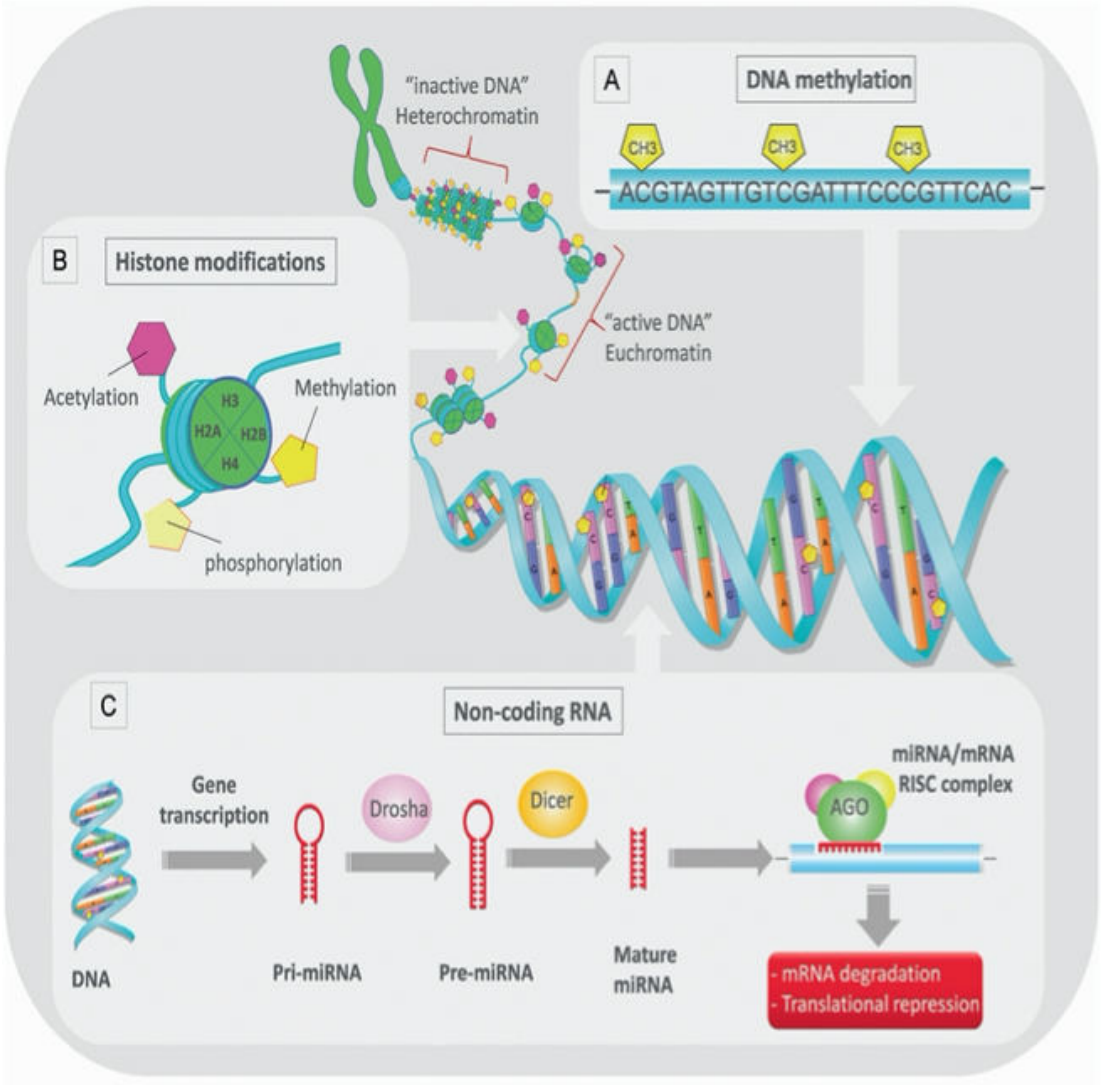

Fig. 5. Epigenetic modifications of miRNA in a mammalian system [12].

miR-21 is thought to be suitable for miRNA-based therapeutics as it plays a role in lowering blood pressure [20]. miR-126a-5p plays a role in the hypoxia-mediated endothelial migration of neonatal pulmonary hypertension [2]. In another study, it was concluded that miR-17 regulates the Th1 reaction and the production of interleukin-10. Moreover, miR-15 expression was reported to increase the induction of T cells [21]. In a study, it was reported that miR-223 expression levels decreased in the lungs, arteries and smooth muscle cells of hypertensive patients and this decrease was regulated by HIF-1 alpha activity. As a result of this regulation, it was concluded that PARP-1 activity was upregulated and had a positive effect on endothelial dysfunction [22]. Another study concluded that miR-223-3p targets ITGB3 and ıık of PAH [26]. In miR-1 essential hypertensive patients and pre-eclampsıas are upregulated in peripheral blood mononuclear cells [24].

miRNA is known to play an important role in the development of hypertension as well as preventive and reparative therapeutics for hypertension. Vascular smooth cells (VSMC) enable the formation of the medial layer of the vessels. miRNAs play an important role in VSMC development, phenotype and transcriptional regulation [4].

miR-145 is known to play an important role in the development of the cardiovascular system as a regulator. It has also been reported that mir-145 is required for VSMC differentiation [1]. It is also known that miR-9 and miR-126 are closely related to EH in humans and that these miRNAs are associated with the prognosis of target organ damage in hypertensive patients [4].

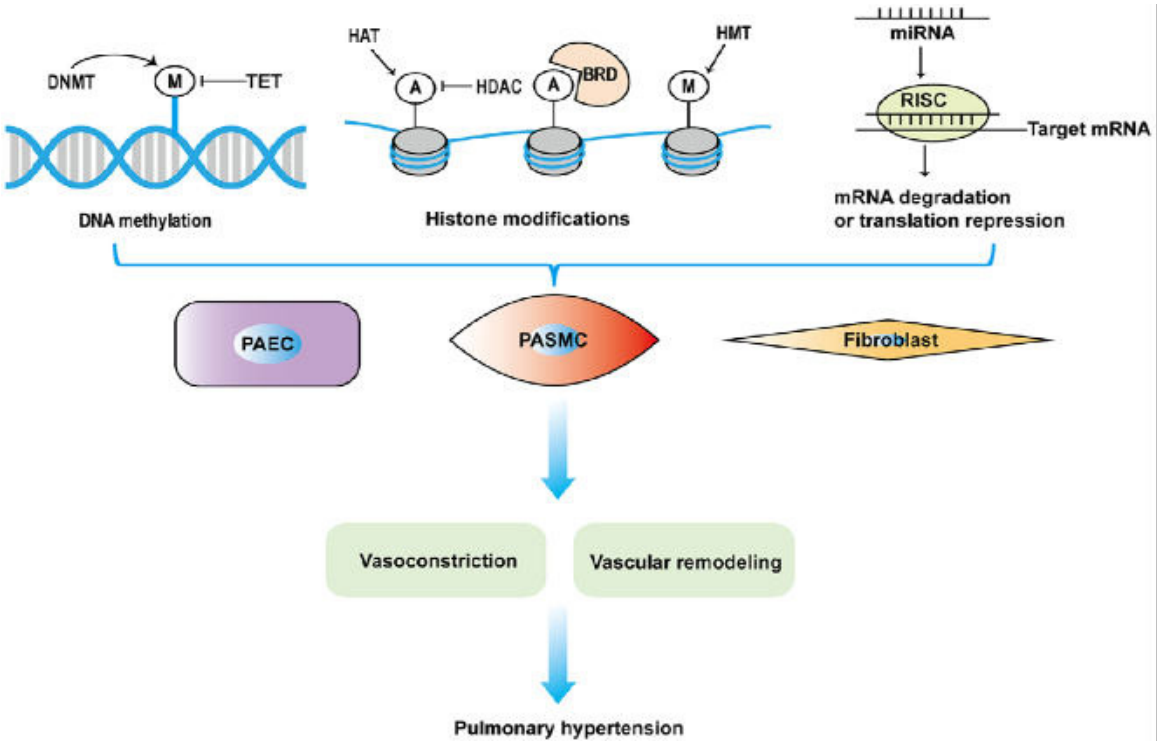

Fig. 4. Schematic overview of the miRNA pathway [10].

Endothelial cells contribute to the pathogenesis of hypertension by secreting many substances. One of them is nitric oxide. Nitric oxide is involved in maintaining normal blood pressure. It is known that there is a relationship between impaired nitric oxide activity in hypertension and increased arterial tone, but its mechanism is still not understood. It acts as a biomarker in the diagnosis of many diseases such as cardiovascular diseases. miR-155 can be useful in preventing the development of hypertension by regulating the endothelial nitric oxide synthase (eNOs) enzyme [25]. On the other hand, in one study, it was concluded that miR-155- 5p caused vasorelaxation impairment by down-regulation of eNOS found in endothelial cells [26]. It has been reported that miR-100 targets the rs6186923 polymorphic region of the TRB3 gene and consequently affects hypertension and left ventricular hypertrophy. However, the researchers argue that rs6186923 should be verified with miR-100 western blot and evaluated further in future studies [27].

It is known that miR-140-5p expression is decreased in both PAH patients and rat monocrotolin-induced PAH models. SMURF1 and DUMT have been found to be direct target genes of miR-140-5p in pulmonary artery smooth muscle cells (PASMCs) and play a role in the pathogenesis of PAH. In the same study, it was found that the target genes of miR-140-5p contributed to PAH-related biological processes such as biological regulation, metabolic process, cell communication, and response to chemical stimuli [28]. It is known that the combination of miR-199a-3p, miR-208a-3p, miR-122-5p and miR 223-3p is a marker for the diagnosis of hypertension and that miRNA dysregulation increases the risk of hypertension [29]. A study from exosomes concluded that hsa-miR-210 is secreted through exosomes that play a role in the pathomechanism of the disease [30].

Li *et al*. [31] reported that miR-124 is down-regulated in cells exposed to hypoxia. It was observed that the level of mRNA expression normalized with miR-124 was lower in PASMCs originating from PAH and COPD compared to the control group, and it was concluded that miR-124 may play a role in the pathogenesis of PAH in COPD patients. In the same study, PASMCs were subjected to hypoxia, and miR-124 was observed to be significantly downregulated, and GRB2 mRNA expression was found to be significantly upregulated in cells exposed to hypoxia relative to cells exposed to normoxia [31].

Hypertension is a multifactorial cardiovascular disease. Stroke is an important risk factor for the development of coronary artery disease, heart factor, and chronic kidney factor [1, 2]. miRNA are small non-coding RNAs that are approximately 16-25 bp long. There is a relationship between miRNAs and hypertension in several ways. It is known that miRNAs play an important role in the pathogenesis of hypertension. Recently, scientists have focused on miRNA and hypertension relationships. Studies by many scientists have shown that expression levels of miRNAs are involved in different biological processes [2, 5]. There is also a relationship between miRNAs and hypoxia. In hypertensive patients, miR-21 can be used as a new therapeutic target against the development of atherosclerosis, and studies have also found that miR-214 is a novel therapeutic target as it is a promising diagnostic tool [5].

It has also been reported that many miRNAs such as miR-210, miR-124, miR-204 and miR-138 regulate SMC gene expression in PAH due to hypoxia [32]. Also, as a result of recent studies, miR 223-3p, miR-27a, miR-150 could be new therapeutic targets for PAH [23, 26]. In addition, it was concluded that NO, which is associated with hypertension, contributes to the prevention of hypertension [4]. Finally, the regulatory effect of miRNAs on epigenetic expression has been more and more known in recent years [1]. miRNAs also target epigenetic-related enzymes and the expression of epigenetic mechanism components [13]. miRNAs can be used as biomarkers for hypertension [1].

CONCLUSION

As a result, miRNA plays a crucial role in the development of HTN and has the potential to target these miRNAs as preventive and restorative therapy for HTN. The relationship, effects and importance of miRNAs on hypertension are discussed in this review. In the future, miRNAs are thought to be a solution to diseases such as hypertension and may be effective in the diagnosis and treatment of diseases.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during the conduction or writing of this study.

Authors' Contribution

Study Conception: NA; Study Design: NA, OT; Supervision: NA, ÖSY; Literature Review: NA, OT; Manuscript Preparation: NA, OT and Critical Review: NA, ÖSY.

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Use of del Nido cardioplegia in adult cardiac surgery

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ABSTRACT

In most adult cardiac surgery operations, the heart must be completely immobile and isolated from the blood. Therefore, the heart is stopped in diastole and a still operative site is obtained. Cardiac arrest results in ischemia-reperfusion injury. For these reasons, myocardial protection and the prevention of damages are required. Various cardioplegia solutions are used for this purpose. It can be said that cardioplegia is the gold standard method of myocardial protection in cardiac arrest. Nowadays, "Single-dose cardioplegia" applications are increasingly used, especially in minimally invasive cardiac surgery and basic coronary bypass procedures due to the advantages they provide, which include reduction of aortic cross-clamp time, prevention of frequent interruption of the procedure due to cardioplegia, and reduced postoperative myocardial dysfunction incidence. The two main solutions used in single dose cardioplegia applications are the Bretschneider solution and the del Nido extracellular cardioplegia solution. The del Nido cardioplegia solution (dNCS), which was originally developed for use in pediatric cardiac surgery, has recently increased its use in adult cardiac surgery due to straightforward application and long-term effectiveness. The del Nido cardioplegia reduces the aortic cross clamp duration, cardiopulmonary bypass time and required cardioplegia solution volume, and is a safer and superior cardioplegia solution and technique in terms of myocardial protection with regards to many organs and cardiac-biochemical parameters.

Keywords: Del Nido cardioplegia, adult cardiac surgery, myocardial protection, cardioplegia, cardiopulmonary bypass

In most cardiac surgery operations, the heart must be completely immobile and isolated from the blood. Cardiac arrest and reperfusion also bring about myocardial damage. For these reasons, various protective and preventive measures have emerged for myocardial protection [1], including cardioplegia and non-cardioplegic methods, some of which include hypothermia, fibrillatory arrest and ischemic preparation / preconditioning. Cardioplegia, otherwise known as the pharmacological method, is achieved with cardioplegic solutions. It is an essential and indispensable method of myocardial protection in all cardiac surgery

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procedures in which the heart must be stopped [2].

Crystalloid and blood cardioplegia are used for conventional cardioplegia. Its effectiveness was tried to be increased by various additives to the solutions [3, 4]. A good and effective cardioplegia solution must be able to provide a rapid diastolic arrest to reduce the use of high energy phosphate compounds (Adenosine Triphosphate [ATP] and phosphocreatine) in myocardial cells. In addition, it should prevent permanent damage by reducing reperfusion damage in myocardial protection [5]. There are many cardioplegia solutions and application methods. The purpose is to allow the safe application of cardiac surgery, ensure that the patient safely exits from cardiopulmonary bypass and to prevent any damage and toxic effect to the heart and all other organs in the postoperative period [6]. Diversity and research in this field have increased because of the differing contents used in the preparation of cardioplegia solutions for myocardial protection for many years [7, 8]. One of the current and effective cardioplegic solutions used in recent years is the del Nido cardioplegia solution (dNCS).

In this study, we aimed to discuss the use of dNCS in adult cardiac surgery in light of the current literature.

History

The scientists who pioneered the development of cardioplegia are Bretschneider, Spieckman, Kirsch, and Hoelscher. The concept of stopping the electromechanical activity of the heart came to the fore in the 1950s to reduce ischemia reperfusion injury. At that time, the cardioplegic agent used was Melrose solution [9].

The dNCS was first used in Boston Children's Hospital. This solution, which was originally developed for use in pediatric and pediatric cardiac surgery [10, 11] has now become widespread in adult cardiac surgery. In the early 1990s, researchers at the University of Pittsburgh, Pedro del Nido, Hung Cao-Danh, K. Eric Sommers, and Akihiko Ohkado, developed a new cardioplegia solution for myocardial protection called the dNCS in the literature and clinical practice [12]. The dNCS has been used successfully in adult cardiac surgery since 2003 [13].

Structure and Metabolism of the Myocardium

The main contractile unit of the myocardium are myocytes. The basal membrane, located on the inner and outer layers, connects myocytes to each other and the external environment. The sarcolemma with myofibril content surrounding the myocytes is located under the basement membrane. Myofibrils consist of actin and myosin. These myofilaments ensure the contraction and pumping function of the heart. There are many mitochondria in myocardial cells. Having a large number of mitochondria is of great importance for aerobic respiration [14].

The energy required for the contraction of the heart muscle is obtained from ATP. In cases of ischemia and hypoxia, the necessary energy is provided by glycogen. When aerobic metabolism cannot provide enough energy, anaerobic glycolysis takes over. Adenosine monophosphate and lactate accumulates in anaerobic metabolism. Energy synthesis is inhibited by the accumulation of lactate. Under normal conditions with energy deficit, the phosphofructokinase enzyme is active, however, in ischemic conditions it is not activated, and glucose production does not occur. Consequently, cell destruction and hypoxia are observed [15, 16].

Myocardial Protection

Preservation of the myocardium is the most fundamental point of cardiac surgery. Myocardial protection is important both during and after the operation in terms of preserving hemodynamic conditions and preventing morbidity and mortality. Myocardial protection is provided by mechanical and pharmacological methods. Since the myocardium is subject to prolonged ischemia in cardiac surgery, special attention should be paid to the protection of myocardium and endothelium. Cardioplegic solutions are used to prevent myocardial dysfunction due to ischemia during and after cardiac surgery. Choosing the appropriate cardioplegia solution is particularly important to prevent ischemia-reperfusion injury and related adverse events [17].

Cardioplegia

Cardioplegia is a current and important myocardial protection method. It is the gold standard of myocardial protection in cardiac arrest. Cardioplegic solutions are hyperkalemic, which creates a depolarized positive resting state that brings about arrest. Cardioplegic arrest reduces myocardial oxygen and energy consump-

tion. Cardioplegia solution stops the heart rapidly in diastole and consequently reduces the energy consumption of myocardial cells and ischemia-reperfusion damage [18].

The mechanisms required for a cardioplegic solution to provide effective protection are as follows [19]:

1. *Arrest:* To reduce energy consumption and relieve myocardium, diastolic arrest should be fast and effective.
2. *Protection:* To protect the myocardium, ischemia-reperfusion damage must be minimized, and irreversible damage, prevented.
3. *Reversibility:* The functions of the heart should be able to restart quickly, easily, and effectively.
4. *Minimum toxicity:* It should have minimal toxic effect on the heart and all other organs postoperatively.

Del Nido Cardioplegia Solution (dNCS)

Many cardiac surgeries can be performed easily under cardiac arrest with cardioplegia. Although the dNCS has been used in pediatric surgery centers for many years, it has recently been used in adult cardiac surgery as well. The straightforward application of del Nido cardioplegia solution and its long-term effectiveness have increased its use in adult cardiac surgery [20]. In addition, it has been shown to provide 9,300 dollars of cost advantage in 100 cases [21].

Adult dNCS is an extracellular solution mixed with autologous blood obtained from the extracorporeal circuit. The crystalloid to blood ratio is 4:1. The dNCS protocol for adult patients is 20 ml/kg with a maximum dose of 1000 mL for patients weighing 50 kg or more. It provides effective myocardial protection for around 90 minutes. If the aortic cross clamp time is expected to be less than 30 minutes, a half dose of the dNCS is used to arrest the heart. After 90 minutes of aortic cross clamping, it should be decided how much dNCS will be given again depending on the duration of the surgical procedure to be performed. The application pressure of cardioplegia should be at the level of 100-200 mmHg. The dNCS is given as cold cardioplegia at 4°C. It can be administered antegradely or retrogradely. Additional doses of the dNCS may be given in patients with aortic insufficiency, hypertrophic hearts, coronary disease and in cases where the effectiveness of the given dose is insufficient [20].

In the preparation of the crystalloid component of the dNCS, Plasma-Lyte A, mannitol, magnesium sulfate, bicarbonate, potassium, and lidocaine are used (Table 1). The pH of the solution is 7.4. A modified 1000 mL dNCS comprises 200 ml blood (4:1) in a balanced solution containing 26 mEq/L potassium chloride, 6.5 mL 2% lidocaine, 17 mL 20% mannitol, 14 mL 15% magnesium sulfate, and 13 mEq/L sodium bicarbonate (Table 2) [13].

Plasma Lyte A: It is a basic solution with a pH value of 7.4 containing 140 mmol/L sodium, 5 mEq/L potassium, 3 mEq/L magnesium, 98 mEq/L chloride, 27 mEq/L acetate, and 23 mEq/L gluconate:

1. *Mannitol:* Balances osmotic pressure and acts as a free radical scavenger.
2. *Magnesium sulfate:* It is a natural calcium channel blocker and provides myocardial healing.
3. *Sodium bicarbonate:* Used as a buffer to re-

Table 1. Original del Nido cardioplegia solution content

Content	Volume
Plasma-Lyte A	1000 mL
Mannitol 20%	16.3 mL
$MgSO_4$ 50%	4 mL
$NaHCO_3$ 8.4%	13 mL
KCL 2 mEq/mL	13 ml
Lidocaine 1%	13 mL
Patient blood	200 ml (20% of del Nido cardioplegia solution)

Table 2. Modified del Nido cardioplegia solution content

Content	Volume
Balanced electrolyte solution	1000 mL
Mannitol 20%	17 mL
$MgSO_4$ 15%	14 mL
$NaHCO_3$ 8.4%	13 mL
KCL 1 mEq/mL	26 mL
Lidocaine 2%	6.5 mL
Patient blood	200 ml (20% of del Nido cardioplegia solution)

move excess hydrogen ions and maintain intracellular pH.

4. *Potassium chloride:* Induces myocardial depolarization

5. *Lidocaine:* Used as a sodium channel blocker and hyperpolarizing agent. Provides sufficient concentration to continuously affect myocardium

6. *Patient blood:* 20% of Del Nido cardioplegia is the patient's fully oxygenated blood. Protects aerobic metabolism and provides buffering to ensure anaerobic glycolysis.

Kantathut *et al*. [22] investigated the use of lactate Ringer's instead of plasma Lyte A, which is the basic solution for the dNCS. They stated that plasma Lyte A is not found in many countries, which prevents the use of the dNCS. In their study, they used lactat Ringer's solution instead of plasma Lyte A and aimed to evaluate its effect on myocardial protection and clinical results. They reported comparable results with dNCS with plasma Lyte A and stated that cardiac surgery centers which could not obtain plasma-Lyte could use lactate Ringer's as an alternative [22]. Many cardiac surgery centers now use a balanced solution instead of plasma Lyte A in modified dNCS.

Advantages and Disadvantages of del Nido Cardioplegia Solution

Advantages

Many studies involving cardiac surgeries performed with dNCS report that it is a safer and superior cardioplegia solution and technique in terms of aortic cross clamp duration, cardiopulmonary bypass time, required cardioplegia solution volume and cardiac and many organ and biochemical parameters [23- 25]. In a meta-analysis including 5516 patients from 10 randomized controlled studies, including a larger patient and study series, and 13 cohort studies with propensity-score match analysis, authors revealed that dNCS shortened operation times compared to multidose cardioplegia, while decreasing reperfusion-related fibrillation rates, and postoperative cardiac enzyme levels [26]. Subsequently, in a study, microembolism was scanned by monitoring with transcranial Doppler ultrasonography and middle cerebral artery control at the time of cardioplegia and crossclamping. This study revealed that the single dose dNCS strategy led to less cerebral microembolism compared to conventional multi-dose cardioplegia [27].

In a systematic review and meta-analysis including one randomized controlled trial, 7 revised observational studies, and 5 uncorrected observational studies conducted between 1996 and 2017; the authors found no difference between the groups in terms of in-hospital mortality [28]. Aortic crossclamp time, CPB times, cardioplegia volume and postoperative troponin levels were lower in the dNCS group. Based on these results, the authors concluded that dNCS could be a safe alternative to blood cardioplegia and potentially provide better myocardial protection [28].

Disadvantages

There are also some concerns related to the dNCS. One of the major problem is that the dNCS solution has about 300 variations of the formula with the same name but with different chemical combinations. In coronary artery disease, a uniform distribution is not guaranteed owing to the presence of diffuse vessel disease and impaired microcirculation. Residual potassium due to the high potassium content of dNCS may cause coronary vasoconstriction and consequently complicate myocardial ischemia [29]. Also the dNCS has a low nutrient content of 21 kcal/L. An energy-depleted myocardium will be affected by low energy levels [30]. And, infusing multiple doses of dNCS may lead to increased myocardial concentration of lidocaine, resulting in lidocaine toxicity, which is associated with peripheral vasodilation, negative inotropy, ventricular arrhythmias, and seizure [31].

Storage of del Nido Cardioplegia Solution

In clinics where dNCS is used, it is prepared in the hospital just before surgery. After obtaining information about the efficiency and reliability of the studies, studies were carried out on the storage conditions. Lackner *et al*. [32] investigated the storage of lidocaine in glass and polyvinyl chloride (PVC) containers in solutions containing potassium chloride, sodium bicarbonate, dextrose, and sodium chloride. Lidocaine concentrations were significantly reduced in PVC bags stored at 22°C and underfilled PVC bags stored at 4°C. The authors concluded that the lidocaine structure remained stable when the solutions were stored in glass containers or large-volume PVC containers in the refrigerator [32]. Pereira *et al*. [33] reported that the lidocaine concentrations in dNCS solutions stored in ethylene-vinyl acetate (EVA) bags for 30 days at

4°C remained 95.8% but decreased to 67% within 30 days at 35°C and 50% was lost within 30 days at 70°C. The authors stated that dNCS was stable for at least 30 days under 4°C cooling in EVA bags [33].

Křížek *et al*. [34] conducted an up-to-date study, in which possible chemical changes in the content of cardioplegia solution according to the content of the storage material and the elapsed time were investigated. Six different dNCS were prepared based on the content of magnesium ions and sodium bicarbonate, which were kept in EVA bags or glass storage containers. All these variants were evaluated for stability while stored at 4°C, 22°C and 50°C. The concentrations of the components were monitored using high pressure liquid chromatography and capillary electrophoresis, and it was found that dNCS remained stable for 8 weeks at 4°C, and replacement of magnesium chloride with magnesium sulfate and/or presence of sodium bicarbonate had no effect on stability. It has also been shown that if the dNCS was not cooled or kept at a high temperature, the concentration of lidocaine in the solution stored in EVA bags may change significantly with the adsorption of lidocaine to the infusion bag material (within 25 days, the lidocaine concentration dropped to half of its original value). Therefore, the authors concluded that dNCS stored in EVA bags should be kept at 4°C to prevent changes in its pharmacological effect [34].

CONCLUSION

In adult cardiac surgery operations, the dNCS is more advantageous than other cardioplegia solutions in many ways. Many studies report that dNCS reduces aortic cross-clamp duration, cardiopulmonary bypass time and required cardioplegia solution volume, is a safer and satisfactory cardioplegia solution in terms of myocardial protection, many organs, and cardiac-biochemical parameters. The del Nido cardioplegia can be used as a safe and effective solution in adult cardiac surgery.

Authors' Contribution

Study Conception: BA; Study Design: BA, MS, SB, FK; Supervision: AKA, MS, OG, MTG, ME; Funding: AKA, ME; Materials: MS, SB, FK; Data Collection and/or Processing: BA, ME; Statistical Analysis and/or Data Interpretation: BA, MS, SB, FK, OG; Literature Review: BA, ME; Manuscript Preparation: BA, MS, SB, FK, AKA, MS, OG, MTG, ME, ŞY and Critical Review: BA, MS, SB, FK, AKA, MS, OG, MTG, ME, ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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