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Evaluation of Serum Vitamin A, Vitamin E, Cholesterol, and Triglyceride Levels in Pregnant Women Diagnosed with Missed Abortion

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ABSTRACT

Introduction: Missed abortion is defined as the intrauterine death of an embryo or fetus. It occurs when there is no fetal heartbeat, but it does not result in bleeding or miscarriage. It accounts for approximately 15% of all pregnancies. Studies have linked the risk of early pregnancy loss to poor vitamin intake. Essential micronutrients in the human body, vitamin A and E, play crucial roles in maternal health and embryonic development. Cholesterol is presumed to play a role in human fertility because it is the main substrate of steroid synthesis. Studies have reported that normal lipid metabolism plays a role in pregnancy complications, such as endothelial damage and spontaneous miscarriage. Maternal hypercholesterolemia is linked to umbilical cord endothelial dysfunction. Additionally, dysregulation of fat metabolism characterized by significantly increased total cholesterol (TC) and triglyceride (TG) levels induces low-grade inflammation.

Methods: The study, conducted at the İstanbul Training and Research Hospital from 01.02.2023 to 01.08.2023, included blood samples obtained from 50 pregnant women aged 20-45, diagnosed with a missed miscarriage. The vitamin A, E, TC, and TG values of the blood samples were compared.

Results: Comparison of vitamin A, vitamin E, TC, and TG measurement values between the healthy and missed diagnosis groups in early pregnancy did not reveal significant differences. This study was designed to analyze serum vitamin A and E levels, cholesterol, and TG levels, potentially leading to early embryo and fetal losses, to assess the nutritional status and vitamin supplementation in early pregnancy. Due to the insufficient number of studies in the literature, further research with a larger sample size is needed.

Conclusion: In our study, no association was found between maternal serum levels of vitamin A and E, TC, TG, and missed abortions in early pregnancy.

Keywords: Missed abortion, vitamin A, E, total cholesterol, triglyceride

Introduction

Missed abortion is defined as the intrauterine death of an embryo or fetus. It occurs when there is no fetal heartbeat, but it does not result in bleeding or miscarriage. It accounts for approximately 15% of all pregnancies (1). Studies have linked the risk of early pregnancy loss to poor vitamin intake. Because the mother's nutritional status can influence the baby's development, vitamin supplementation is important for pregnant women and those planning pregnancy (2). Essential micronutrients in the human body such as vitamin A and E play crucial roles in maternal health and embryonic development (3,4).

Vitamin A is required for the growth and proliferation of epithelial cells (5). Vitamin A deficiency can lead to night blindness, pregnancy complications, an increase in fetal malformations, and affect embryonic development (6). In particular, it directly affects reproduction, the ability to conceive, and the healthy progression of pregnancy in ruminants (7).

Vitamin E is essential for maintaining metabolic functions in the human body and acts as an antioxidant by scavenging free radicals (3). Owing to its antioxidant effects, it protects tissues by preventing the oxidation of intracellular and intercellular membranes, thereby allowing them to function properly (8). Vitamin E deficiency in pregnant women can lead to placental aging, vascular endothelial damage, hypertensive disorders of pregnancy, early placental separation, miscarriage, and preterm birth, among other complications (9).

Cholesterol is presumed to play a role in human fertility because it is the main substrate for steroid synthesis (10). Studies have reported that normal lipid metabolism plays a role in pregnancy complications,

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such as endothelial damage and spontaneous miscarriages (11). Maternal hypercholesterolemia has been linked to umbilical cord endothelial dysfunction (12). Additionally, dysregulation of fat metabolism characterized by significantly increased total cholesterol (TC) and triglyceride (TG) levels induces low-grade inflammation (13,14). Temporary hypercholesterolemia is a physiological process that provides adequate cholesterol for fetal growth and meets the mother's energy needs during pregnancy (15). TC levels <280 mg/dL indicate maternal physiological hypercholesterolemia, while levels ≥280 mg/dL or TC levels above the 75th percentile in different trimesters of pregnancy indicate maternal supraphysiological hypercholesterolemia (MSPH) (16). The potential effects of MSPH on the placental microvascular system are not well understood. Endothelial dysfunction of both macro- and microvascular vessels in the placenta during pregnancy may be associated with MSPH (16,17).

This study was designed to analyze serum vitamin A and E levels, cholesterol, and TG levels, potentially leading to early embryo and fetal losses, to assess the nutritional status and vitamin supplementation in early pregnancy.

Methods

Our study was conducted using blood samples obtained from pregnant women who presented to University of Health Sciences Türkiye, İstanbul Training and Research Hospital and received approval from the Institutional Review Board (approval number: 54, date: 10.03.2023). A total of 50 pregnant women were included in the study, comprising 25 women with a diagnosis of missed abortion in the first trimester and 25 healthy controls. An informed consent form was obtained from the patients.

The exclusion criteria for the study involved patients with systemic illnesses, uterine anatomical abnormalities, multiple pregnancies, multivitamin supplement use, and in vitro fertilization. None of the selected pregnant women used multivitamins because this was one of the exclusion criteria.

Serum levels of vitamins A and E, TC, and TG were assessed in each pregnant woman. The following data were also recorded for the patients: age, gravidity, parity, number of previous miscarriages, height, weight, body mass index (BMI), and gestational age measured during ultrasonographic examination.

Laboratory work was conducted at the İstanbul Training and Research Hospital Biochemistry Laboratory. Blood samples were collected in monette tubes after a fasting period of 10-12 hours, were centrifuged at 4000 revolutions per minute for 10 min, and the levels of TC and TG were determined using the Roche Cobas c 501 analyzer (California, USA). Vitamin A and E levels were analyzed at the İstanbul Training and Research Hospital Biochemistry Laboratory. A separate blood sample was collected in a monette tube, and 1 mL of ethyl alcohol was added to 0.3 mL of serum. The mixture was vortexed for thorough mixing. Subsequently, the mixture was centrifuged at 2000 revolutions per minute for 3 min, and 0.2 mL of n-hexane was added to the upper layer. This step allowed the extraction of vitamins A and E into the n-hexane phase. The extraction process was repeated twice, and the combined n-hexane phases were evaporated under nitrogen gas until dry. The residue in the tube was dissolved in 0.2 mL of methanol and prepared for analysis by high-performance liquid chromatography (HPLC-10) (Nashua, New Hampshire, USA). Vitamins A and E were determined using an octadecyl-silica-2 HPLC column (Nashua, New Hampshire, USA) with a mobile phase consisting of methanol: acetonitrile: chloroform (47:42:11, v/v). The flow rate of the mobile phase was set at 1 mL/min. Vitamin E and vitamin A were determined at 296 and 326 nm, respectively. In cases of inappropriate or suspicious results, samples were retested.

Statistical Analysis

Descriptive statistics such as mean, standard deviation, median, minimum, maximum, frequency, and percentage were used to describe the data. The distribution of variables was assessed using the Kolmogorov-Smirnov test. For the analysis of quantitative independent variables, the Mann-Whitney U test was employed. For the analysis of qualitative independent variables, the chi-square test was used, and in cases in which the conditions for the chi-square test were not met, the Fisher's exact test was applied. Statistical analyses were conducted using SPSS version 28.0.

Results

The study included a total of 50 cases. The ages of the patients ranged from 20 to 45 years, with a mean age of 30.1±6.0 years. The mean BMI of pregnant women who participated in the study was 23.5±1.9. Among the participants, 25 had no fetal heartbeats detected during the ultrasound examinations, whereas 25 did have fetal heartbeats. The gestational age of the pregnant women included in the study ranged from 6.4 to 12.0 weeks, with an average of 8.8±1.8 weeks. All participants (100%) had spontaneous pregnancies. None of the patients had comorbid diseases or were taking medications. Among the participating pregnant women, 43 (86.0%) had no history of previous miscarriages, whereas 7 (14.2%) had a history of medical abortions. The mean laboratory values obtained from our study were as follows: Vitamin A: 465±165 ng/mL, vitamin E: 12.5±3.6 ng/mL, cholesterol: 160±25.2 mg/dL, TG: 99.2±35.4 mg/dL.

In the ultrasound examination, patients without fetal heart activity (FHA) were classified as having missed abortion and were compared with the control group with FHA.

Between the groups with and without FHA, there were no significant differences in age, BMI, gravidity, parity number, parity rate, number of previous miscarriages, miscarriage rate, or mode of delivery in the previous pregnancy ($p>0.05$).

The gestational age determined by ultrasound was similar in both groups, with a mean of 8.1±1.3 weeks in the control group with FHA and 8.3±1.2 weeks in the group without FHA, and the difference was not statistically significant ($p>0.05$).

The levels of vitamin A were 445±210 ng/mL in the group without FHA and 485±102 ng/mL in the control group, and there was no statistically significant difference in vitamin A levels between the two groups ($p>0.05$).

Vitamin E levels were measured as 12.4±4.2 ng/mL in the group without FHA and 12.5±3.0 ng/mL in the control group, with no statistically significant difference in these values between the two groups (p>0.05).

The TC levels, the group with missed abortion had levels of 159±27.6 mg/dL, whereas the control group had levels of 160±23.1 mg/dL. The TG levels were 98.0±35.3 mg/dL in the group with missed abortion and 100±36.3 mg/dL in the control group. There were no significant differences in TC and TG levels between the two groups (p>0.05) (Table 1).

Discussion

This study, conducted with a total of 50 cases, examined the clinical and laboratory characteristics of missed abortions. The average age and BMI of the patients reflected the general characteristics of the pregnant women in the study. Our findings indicated that the influence of age and BMI on the incidence of missed abortions was not statistically significant. According to the results of the ultrasound examination, there was no significant difference in gestational weeks between the groups with and without FHA. The gestational age of pregnant women without FHA was similar to that of the control group. The study also investigated the impact of vitamin A and E levels on the incidence of missed abortions. Our findings showed no significant difference in these vitamin levels between the two groups, indicating that vitamin A and E levels may not be determinants of the risk of missed abortion.

We conducted a literature search but did not find sufficient studies that correlated vitamin A, E, TC, and TG levels with early pregnancy losses.

In a study by Chen et al. (18), in contrast to our study, the authors found that vitamin A levels were low and vitamin E levels were high in early pregnancy.

Vitamin A deficiency has been reported to lead to early pregnancy loss and weak births in cattle (19).

Meng et al. (20) reported normal levels of vitamin E in early pregnancy, similar to our study.

A study by Shamim et al. (21) conducted on pregnant women in rural Bangladesh reported that low plasma α-tocopherol levels and the mother's vitamin E status in the first trimester could affect the risk of early pregnancy loss.

In 2013, Sönmez (22) reported early pregnancy loss in rats with vitamin E deficiency.

Amundsen et al. (23) reported no difference in TC and TG values in early pregnancy in pregnant women with live fetuses, similar to our study in which both groups had normal TC and TG values.

Vrijkotte et al. (24) found no relationship between TC and TG levels and fetal loss in early pregnancies, consistent with our study.

Wang et al. (25) found higher TC and TG levels in early pregnancy among pregnant women with adverse pregnancy outcomes. In contrast, our study did not find statistically significant differences in TC and TG levels between the FHA and missed abortion groups (25).

Study Limitations

Due to the insufficient number of studies in the literature, further research with a larger sample size is needed. The number of patients and controls in this study is one of the limitations of this study. In addition, the fact that its difference from other results in the literature has not been clearly determined indicates that more work should be performed in this direction.

Table 1. Comparison of serum vitamin A, vitamin E, cholesterol, and triglyceride levels among pregnant women diagnosed with missed abortion

		FHA (-)		FHA (+)		p
		Mean ± SD, (n, %)	Median	Mean ± SD, (n, %)	Median	
Age		29.2±6.2	28.0	31.0±5.8	30.0	0.176[m]
BMI		23.8±1.5	22.1	24.1±2.1	23.5	0.006[m]
Gravity		2.2±1.2	2.0	2.6±1.5	2.0	0.488[m]
Parity		1.04±0.89	1.00	1.4±1.5	1.00	0.663[m]
Parity	(-)	7 (28.0%)		10 (40.0%)		0.370[x²]
	(+)	18 (72.0%)		15 (60.0%)		
Abortus		0.28±0.68	0.00	0.12±0.44	0.00	0.240[m]
Abortus	(-)	20 (80.0%)		23 (92.0%)		0.221[x²]
	(+)	5 (20.0%)		2 (8.0%)		
Delivery type	NSD	17 (68.0%)		18 (72.0%)		0.758[x²]
	CS	8 (32.0%)		7 (28.0%)		
USG week		8.3±1.2	10.1	8.1±1.3	8.0	0.116[m]
Vitamin A		445±210	400	485±102	484	0.118[m]
Vitamin E		12.4±4.2	11.2	12.5±3.0	12.0	0.322[m]
Cholesterol		159±27.6	155	160±23.1	154	1,000[m]
Triglyceride		98.0±35.3	92.0	100±36.3	90.0	0.854[m]

[m]Mann-Whitney U test, [x]Chi-square test, BMI: Body mass index, FHA: Fetal heart activity, NSD: Normal spontaneous delivery, CS: Cesarean section, USG: Ultrasonography, SD: Standard deviation

Conclusion

This study comprehensively analyzed the clinical and laboratory characteristics of missed abortions. The findings suggest that age, BMI, gestational age, and laboratory parameters, such as vitamin A and E levels, TC, and TG, may not have a statistically significant impact on the incidence of missed abortion. We found few studies related to our article topic in the literature; therefore, the discussion section is limited. These results could serve as an important reference for future research and clinical applications.

Ethics

Ethics Committee Approval: Our study was conducted using blood samples obtained from pregnant women who presented to University of Health Sciences Türkiye, İstanbul Training and Research Hospital and received approval from the Institutional Review Board (approval number: 54, date: 10.03.2023).

Informed Consent: An informed consent form was obtained from the patients.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.K.K., Concept - A.K.K., A.Ç., Design - A.K.K., C.T., Data Collection or Processing - A.K.K., C.T., Analysis or Interpretation - A.K.K., A.Ç., C.T., Literature Search - A.K.K., A.Ç., C.T., Writing - A.K.K., A.Ç.

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Impact of High-Intensity Interval Training on Bone Metabolism and the Metabolic and Hormonal Profiles of Postmenopausal Women

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ABSTRACT

Introduction: Although many forms of exercise are known to have positive effects on bone metabolism in postmenopausal women, the effect of high-intensity interval training (HIIT) has not been investigated in this setting. This study aimed to evaluate the impact of the 6-week HIIT program on body composition, biochemical parameters, and bone turnover markers in overweight and obese postmenopausal women.

Methods: A total of 32 postmenopausal women were randomly assigned to exercise (n=15) or control (n=17) groups. The blood samples and body composition were analyzed. The exercise group participated in a 6-week stationary bike HIIT exercise [(3 days/week; 30 sec work-90 sec resting intervals with 90-95% of the heart rate reserve-12 to 16 min/day)]. The control group was not involved in any exercise program.

Results: In the exercise group, significant reductions were noted in waist and hip circumference, low-density lipoprotein, total cholesterol, triglycerides, phosphorus, calcium, albumin, bone-specific alkaline phosphatase, type 1 collagen C-terminal telopeptide, and osteocalcin levels, in addition to significant increases in high-density lipoprotein, free thyroxine, thyroid-stimulating hormone, vitamin D (25-hidroksi vitamin D), and cortisol levels, when compared with the control group ($p<0.05$).

Conclusion: Our findings revealed the positive effects of the 6-week HIIT training program in postmenopausal women in terms of reduction in waist and hip circumference, improvement in lipid and hormonal profile, and maintenance of bone metabolism. According to our findings, the 6-week stationary bike HIIT exercise was safe and beneficial for postmenopausal women's health.

Keywords: Bone turnover, CTX, high intensity interval training, menopause, metabolism, osteocalcin

Introduction

During menopause, estrogen levels decrease significantly, leading to various effects on bone tissue, lipid profiles, and glucose metabolism. Estrogen deficiency increases parathyroid hormone (PTH) levels because of decreased bone sensitivity to PTH (1). Additionally, estrogen modifies lipid profiles by boosting high-density lipoprotein (HDL) levels while lowering low-density lipoprotein (LDL) levels, which may contribute to a more atherogenic lipid profile (2). The reduction in estrogen levels during menopause also affects glucose metabolism, decreasing insulin sensitivity, and increasing both insulin secretion and the risk of type 2 diabetes. A major consequence of estrogen deficiency in menopause is rapid bone loss caused by an imbalance between bone resorption and formation. High bone turnover and low bone mineral density (BMD) in osteoporosis can be predicted by biochemical markers such as calcium, PTH, 25-hidroksi vitamin D [25(OH)D], phosphorus, osteocalcin, type 1 collagen C-terminal telopeptide (CTX), and bone-specific alkaline

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phosphatase (Bone-ALP) in which BMD is unavailable (3). Recent studies have suggested that elevated serum PTH, phosphate, and calcium levels during the postmenopausal period may contribute to bone pain and increase the risk of osteoporosis and low BMD (4). Low vitamin D levels further exacerbate this phenomenon by causing secondary hyperparathyroidism and subsequent bone resorption (5). Osteocalcin and Bone-ALP are important markers of bone formation, whereas CTX indicates bone resorption (6,7).

Exercise has been shown to improve physiological and hormonal outcomes in postmenopausal women, positively affecting body composition and bone structure (7,8). Exercise-induced stress stimulates osteoblast activity, promoting new bone formation (7). High-intensity interval training (HIIT) is a popular exercise model that achieves similar benefits to traditional aerobic exercises but in a shorter time (9). HIIT has been associated with better cardiometabolic adaptations and reduced visceral fat in postmenopausal women (10). Despite the known benefits of various exercises on bone metabolism, there are limited data on the effects of HIIT during menopause (11). This study aimed to explore the protective impact of a 6-week HIIT cycling regimen on bone turnover markers, body composition, lipid profiles, and hormonal changes in postmenopausal women.

Methods

Participants

The study included 32 postmenopausal women (age: 53.78±3.93 years, range 48-60 years) diagnosed by a gynecologist. Menopause was defined as the absence of menstruation for at least 12 consecutive months without any other biological cause (12). Sedentarism was defined as self-reported ≤15 minutes of moderate aerobic activity per week (13). Participants were divided into control (n=17) and exercise (n=15) groups. All participants were housewives without a history of tobacco, alcohol, medication, or physical training. The determination of the sample size was based on a power analysis performed using G*Power (3.1.9.2), which yielded an effect size (d) of 1,068 for 95% power at α=0.05, based on Maillard et al. (10).

All participants were evaluated by a family physician and cardiologist. The exercise group was assessed for fitness via treadmill effort testing (NORAV TMX 425, FL, USA) using the modified Bruce protocol (14), with heart rates monitored by GPS (Polar® M400, Finland). Blood pressure was measured according to the American Heart Association Guidelines (15). Following approval from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2017.545, date: 01.06.2018), the participants provided written informed consent, and the study complied with the Helsinki Declaration guidelines.

Study Design

A randomized controlled trial with pre- and post-test assessments was conducted over 6 weeks. Pre- and post-tests were administered between 08.00 and 12.00 a.m., with each participant tested on Tuesday and Friday. On day 1, participants completed a personal information form and an exercise stress test. On day 2, blood samples were collected, followed by anthropometric measurements and body composition analysis. The exercise group underwent a 1-week adaptation phase (30 min/day, 3 days/week) of aerobic cycling, followed by an 18-stage HIIT program for 6 weeks (3 days/week, 25-30 min/day). The control group was excluded from participating in an exercise intervention.

Anthropometric and Body Composition Assessment

Height and weight were assessed using participants dressed in minimal attire and without shoes. Body weights and compositions were determined using a Tanita SC 330 (Tanita Corp., Tokyo, Japan). Participants with body mass index values classified as overweight (25-30 kg/m^2) or obese (≥30 kg/m^2) per World Health Organization standards (16) were included. Measurements of waist, abdomen, and hip circumferences were taken with a 0.1 cm precision using a flexible, non-elastic tape (Rosscraft Innovations Inc., Vancouver, Canada), adhering to the Anthropometric Standardization Reference Manual (17). The waist-to-hip ratio was calculated by dividing the waist circumference by the hip circumference.

On the day of the body composition and biochemical tests, participants were instructed to refrain from exercise for at least 48 h and to fast for 12 h before testing. No dietary restrictions were imposed during the program.

Blood Sample Assessments

Blood samples were collected from the antecubital vein, centrifuged at 3000 x g for 10 min, and the serum was stored at -80 °C until analysis. Total protein, HDL, LDL, triglycerides, cortisol, glucose, insulin, thyroid-stimulating hormone (TSH), free thyroxine (free T4), PTH, phosphorus, 25(OH)D, and total Ca^{++} levels were measured using an automated biochemistry analyzer (Abbot Architect I2000SR and c4000). Bone-ALP (Mybiosource Inc, USA), osteocalcin (Elabscience Co., China, cat no: E-EL-H1343), and CTX (Elabscience Co., China) levels were assessed via ELISA.

High-Intensity Interval Training Protocol

Cycle exercise was chosen to improve the safety of overweight and obese participants. After the pre-tests, the exercise group underwent a 1-week adaptation program (3 days/week, 30 minutes/session) of aerobic cycling (40-45 rpm) using a stationary bike (Profitness 8350-R). The HIIT program was conducted on 3 days/week for 6 weeks. Each session included a warm-up at 70% heart rate reserve (HRR). Training intensity increased biweekly: [weeks 1-2: HRR 90-95% (30 sec work/90 sec rest) x 3 sets (total: 12 min); weeks 3-4: HRR 90-95% x 4 sets (total: 14 min); weeks 5-6: HRR 90-95% x 5 sets (total: 16 min)]. HRR was calculated using the Karvonen et al. (18) method, and intensity was monitored using a cardiac rate monitor (Polar M400, Finland). The program followed the HIIT guidelines of the American College of Sports Medicine (19) for sedentary individuals, and each session was supervised by an exercise specialist.

Statistical Analysis

The mean, standard deviation (SD), minimum and maximum values, and percentage changes between pre- and post-tests [(post- and pre-test)/(pre-test x100)] were calculated. Data were analyzed using SPSS 20.0, with a 95% confidence interval and $p<0.05$ set as significant. The Shapiro-Wilk test was used to assess normality. The Wilcoxon signed-rank test was used for within-group comparisons, and the Mann-Whitney U test was used for between-group comparisons before and after exercise.

Results

Anthropometric and Body Composition Measurements

Descriptive statistics for anthropometric, body composition, biochemical parameters, and bone turnover markers are presented (Tables 1-3). No significant differences were observed between the HIIT (mean ± SD age: 53.42±5.40 years) and control (mean ± SD age: 54.64±5.52 years) groups in the pre-test values, confirming group homogeneity ($p>0.05$).

Body Composition

Within the HIIT group, waist and hip circumferences significantly decreased ($p<0.01$; Table 1), with no significant changes in other body composition metrics ($p>0.05$). The control group exhibited a significant increase in hip circumference ($p<0.05$; Table 1). Inter-group analysis revealed a greater reduction in waist and hip circumferences in the HIIT group compared to controls ($p<0.05$; Table 1), with no significant differences in other body composition parameters ($p>0.05$; Table 1).

Biochemical Parameters

The intra-group analysis showed significant reductions in LDL, total cholesterol (TC), triglycerides (TG), and albumin and increases in HDL, cortisol, TSH, and free T4 levels within the HIIT group ($p<0.001$; Table 2). The control group only exhibited a significant increase in HDL ($p<0.001$; Table 2). Inter-group comparisons indicated that changes in LDL, HDL, TC, TG, cortisol, TSH, free T4, and albumin were more favorable in the HIIT group ($p<0.05$; Table 2). No significant differences were found between the groups for insulin, glucose, and Homeostatic Model Assessment of Insulin Resistance levels ($p>0.05$; Table 2).

Bone Turnover Markers

In the HIIT group, significant reductions were observed in total Ca^{++}, P, Bone-ALP, osteocalcin, and CTX levels, along with an increase in 25(OH)D ($p<0.01$; Table 3), while PTH levels remained unchanged ($p>0.05$; Table 3). In the control group, 25(OH)D, P, Bone-ALP, and PTH levels decreased significantly ($p<0.01$; Table 3), with no significant changes in total Ca^{++}, osteocalcin, and CTX levels. Post-exercise, inter-group analysis showed higher 25(OH)D and P levels in the HIIT group compared to controls ($p<0.01$; Table 3).

Discussion

In postmenopausal women, the 6-week HIIT program, conducted three times per week, significantly improved lipid profiles and bone turnover markers. Notably, waist and hip circumferences were reduced, although no substantial changes were noted in body weight, fat percentage, or lean body mass. These findings are consistent with those of previous studies showing that HIIT can reduce abdominal fat, thereby potentially lowering cardiovascular risk (20,21). The discrepancy observed in other studies could be attributed to variations in exercise duration, frequency, and methodologies, such as longer training periods and differing rest intervals (10,22).

Table 1. Anthropometric and body composition characteristics of both groups (HIIT and control) at baseline and after 6 weeks of training

	HIIT, (n=15)			Control, (n=17)			Baseline differences between groups	Pre-post test differences between groups
	Pre	Post	p[a]	Pre	Post	p[a]	p[b]	p[b]
Height, cm	159.7±5.8 (147-168)	159.8±5.2 (147-168)	0.512	156.8±5.4 (149-167)	156.9±5.0 (149-167)	0.333	0.114	0.114
Weight, kg	84.8±14.4 (63.2-119.1)	85.1±14.4 (60.8-118.4)	0.330	82.5±13.7 (58.9-101.6)	83.0±13.3 (58.9-100.7)	0.393	0.970	0.664
BMI, kg/m^2	33.2±4.9 (27.3-42.2)	33.2±5.0 (26.7-42.3)	0.506	33.2±5.2 (25.9-42.3)	33.4±4.9 (26.0-41.0)	0.409	0.910	0.835
Waist circumference, cm	99.1±10.4 (82.0-117.0)	97.2±10.7 (78.0-117.0)	0.007**	100.9±10.8 (79.0-117.0)	101.9±11.0 (80.0-118.0)	0.064	0.597	0.001**
Hip circumference, cm	120.0±9.8 (105.0-141.0)	118.6±9.5 (104.0-141.0)	0.003**	120.8±10.9 (104.0-140.0)	121.7±11.4 (104.0-140.0)	0.048*	0.940	0.001**
Waist/hip ratio	0.8±0.1 (0.7-0.9)	0.8±0.1 (0.7-0.9)	0.203	0.8±0.1 (0.7-0.9)	0.8±0.1 (0.7-0.9)	0.331	0.955	0.178
Percent body fat, %	41.7±4.8 (32.9-48.4)	42.3±4.5 (32.8-49.5)	0.330	41.6±5.7 (33.7-51.7)	42.6±4.9 (35.5-51.8)	0.062	0.777	0.509
Body fat mass, kg	35.9±9.8 (21.5-57.6)	36.7±9.9 (19.9-58.6)	0.109	34.9±9.9 (21.7-51.9)	35.9±9.5 (22.1-52.2)	0.140	0.955	0.835
Fat-free mass, kg	46.4±4.8 (38.7-58.4)	46.1±4.6 (38.8-56.4)	0.513	45.4±5.2 (34.8-54.0)	44.8±4.5 (34.7-51.6)	0.147	0.955	0.584

Data expressed as mean standard deviations and minimum-maximum. HIIT: High-intensity interval training, BMI: Body mass index, [a]Wilcoxon signed ranks test was performed to compare within groups, [b]Mann-Whitney U test was performed to compare baseline differences between the HIIT and control groups, [b]Mann-Whitney U test was performed to compare pre-post-test differences between the HIIT and control groups. *p<0.05; **p<0.01

Table 2. Biochemical measurements of both groups (HIIT and control) at baseline and after 6 weeks of training

	HIIT (n=15)			Control (n=17)			Baseline differences between groups	Pre-post test differences between groups
	Pre	Post	p[a]	Pre	Post	p[a]	p[b]	p[b]
LDL, mg/dL	187.6±9.2 (174.1-200.8)	175.9±8.1 (164.1-187.6)	0.001**	185.7±9.3 (171.6-200.1)	186.3±9.7 (171.9-200.3)	0.426	0.462	0.001**
HDL, mg/dL	39.7±2.3 (36.3-43.0)	45.2±2.6 (41.2-48.8)	0.001**	39.2±2.3 (35.7-42.8)	39.9±2.3 (36.4-43.2)	0.001**	0.462	0.001**
TC, mg/dL	194.4±9.4 (180.6-207.9)	185.6±8.7 (174.1-198.8)	0.001**	192.4±9.5 178.1-207.2	190.8±11.3 (168.1-205.9)	0.434	0.462	0.001**
TG, mg/dL	143.0±7.1 (132.6-153.2)	136.4±6.6 (127.7-146.3)	0.001**	141.5±7.2 (130.7-152.7)	140.3±8.5 (123.1-151.8)	0.434	0.462	0.001**
Glukoz, mg/dL	93.6±9.2 (80.1-106.8)	91.2±9.1 (76.7-105.9)	0.233	91.6±9.3 (77.6-106.1)	91.3±9.7 (76.8-105.3)	0.400	0.462	0.479
Insulin, µIU/mL	122.2±9.2 (108.8-135.4)	120.8±9.1 (106.4-135.6)	0.609	120.3±9.3 (106.2-134.7)	120.9±9.7 (106.5-134.9)	0.426	0.462	0.479
HOMA-IR	28.4±4.9 (21.5-35.7)	27.4±4.7 (20.1-35.5)	0.427	27.4-4.8 (20.4-35.3)	27.5±5.1 (20.2-35.1)	0.169	0.462	0.485
Cortisol, µg/dL	19.3±2.0 (14.9-22.8)	21.5±2.5 (16.2-25.7)	0.001**	19.6±2.2 (15.5-23.6)	19.7±2.3 (15.8-23.6)	0.980	0.637	0.001**
TSH, mlU/L	2.1±0.8 (2.0-2.2)	2.4±0.2 (2.1-2.6)	0.001**	2.1±0.1 (1.9-2.2)	2.1±0.1 (1.9-2.2)	0.492	0.462	0.001**
T4, µg/dL	9.1±0.3 (8.6-9.5)	9.7±0.7 (8.8-10.9)	0.001**	9.0±0.3 (8.5-9.5)	8.8±0.4 (7.9-9.2)	0.149	0.462	0.001**
Albumin, g/dL	3.4±0.1 (3.2-3.6)	3.3±0.1 (3.1-3.5)	0.001**	3.4±0.1 (3.2-3.6)	3.3±0.3 (2.8-3.7)	0.484	0.462	0.006**

Data expressed as mean standard deviations and minimum-maximum. HIIT: High-intensity interval training, LDL: Low-density lipoprotein, HDL: High-density cholesterol, TC: Total cholesterol, TG: Triglycerides, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, TSH: Thyroid-stimulating hormone, T4: Thyroxine, Ca^{++}: Calcium, PTH: Parathyroid hormone, [a]Wilcoxon signed-ranks test was performed to compare within groups, [b]Mann-Whitney U test was performed to compare baseline differences between the HIIT and control groups, [b]Mann-Whitney U test was performed to compare pre-post-test differences between the HIIT and control groups, *p<0.05; **p<0.01

Table 3. Bone turn-over markers in both groups (HIIT and control) at baseline and after 6 weeks of training

	HIIT (n=15)			Control (n=17)			Baseline differences between groups	Pre-post test differences between groups
	Pre	Post	p[a]	Pre	Post	p[a]	p[b]	p[b]
25(OH)D, ng/mL	30.1±2.1 (27-33.2)	31.2±2.1 (28.1-34.3)	0.001**	29.6±2.1 (26.4-33.0)	29.1±2.1 (25.9-32.5)	0.001**	0.462	0.001**
Total Ca^{++} level, mg/dL	7.0±0.4 (6.4-7.6)	6.6±0.4 (5.9-7.2)	0.005**	6.9±0.4 (6.3-7.6)	6.5±1.2 (4.9-8.7)	0.177	0.462	0.637
P, mg/dL	3.1±0.1 (2.9-3.3)	2.9±0.2 (2.7-3.2)	0.005**	3.1±0.1 (2.9-3.3)	2.8±0.3 (2.4-3.5)	0.006**	0.462	0.005**
PTH, pg/mL	40.5±2.5 (36.9-44.1)	39.9±2.5 (36.1-43.8)	0.281	40.0±2.5 (36.2-43.9)	39.9±2.6 (36.1-43.8)	0.060	0.462	0.485
ALP, u/L	54.8±4.1 (48.7-60.7)	52.0±3.9 (45.8-58.4)	0.009**	53.9±4.2 47.6-60.4	52.1±4.2 (45.8-58.1)	0.001**	0.462	0.282
Osteocalcin, µg/L	8.6±0.4 (8.0-9.2)	8.2±0.4 (7.5-8.8)	0.005**	8.56±0.4 (7.9-9.2)	8.1±1.2 (6.5-10.3)	0.177	0.462	0.637
CTX, ng/mL	0.47±0.22 (0.44-0.50)	0.45±0.23 (0.41-0.48)	0.005**	0.47±0.22 0.43-0.50	0.44±0.07 (0.36-0.56)	0.177	0.462	0.637

Data expressed as mean standard deviations and minimum-maximum. HIIT: High-intensity interval training, ALP: Alkaline phosphatase, CTX: C-terminal telopeptide, [a]The Wilcoxon signed-rank test was used to compare within groups, [b]Mann-Whitney U test was performed to compare baseline differences between the HIIT and control groups, [b]Mann-Whitney U test was performed to compare pre-post-test differences between the HIIT and control groups, *p<0.05, **p<0.01

The absence of dietary restrictions and the use of less advanced body composition measurement techniques, such as Dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI), might have influenced the results. Although HIIT did not significantly alter body fat mass, previous research has shown improvements in abdominal and visceral fat when using more precise measurement techniques (20). Additionally, postmenopausal estrogen deficiency may affect fat oxidation, which could contribute to the observed lack of change in fat mass (23).

Regarding blood lipid profiles, HIIT's effects varied across studies. Although some studies have indicated beneficial effects on lipid profiles in individuals with obesity (21), other studies have shown mixed results (24). In this study, reductions in LDL, TC, and TG, along with an increase in HDL-C, suggest that HIIT positively influences lipid profiles in postmenopausal women.

The hormonal responses to HIIT included increases in TSH, cortisol, and free T4 although these values remained within normal limits. This is consistent with the limited research on the effects of chronic HIIT on these hormones (25). The observed increase in cortisol, TSH, and T4 levels suggests that HIIT stimulates the hypothalamic-pituitary-adrenal and thyroid axes, even after six weeks of training.

The influence of HIIT on bone turnover markers in postmenopausal women is novel given the sparse research in this area. Lester et al. (26) observed no significant changes in Bone-ALP, PTH, 25(OH)D, or CTX after an 8-week aerobic and resistance exercise regimen, despite improvements in BMD. In contrast, Alghadir et al. (27) reported increases in osteocalcin and Bone-ALP levels after 12 weeks of aerobic exercise, suggesting enhanced bone formation. The present study found an increase in vitamin D and significant decreases in bone adenosine monophosphate, calcium, and phosphorus, with no notable change in PTH levels.

The reduction in Bone-ALP levels across both the HIIT and control groups suggests that this change may not be related to exercise. Calcium and PTH are crucial for bone metabolism (28), with PTH responding quickly to fluctuations in serum calcium. The lack of change in PTH levels might be attributed to the timing of serum sample collection, which did not occur within the first 20 minutes after exercise. Furthermore, the decrease in calcium could be linked to a reduction in serum albumin levels (29).

Osteocalcin, a marker of bone formation, and CTX, a marker of bone resorption, both decreased in the exercise group, indicating potential reductions in bone formation alongside decreased resorption. Yamazaki et al. (30) observed a decrease in CTX starting from the third month in postmenopausal women following a daily walking program. Conversely, Villareal et al. (11) noted increases in CTX and osteocalcin in older adults using a combined exercise model and diet, although the effects of exercise on these markers remain unclear.

Study Limitations

These results should be considered with the study's limitations in mind, including the lack of DEXA or MRI for assessing body composition and bone health and the absence of a controlled nutrition program.

Conclusion

The 6-week HIIT program provides significant benefits for postmenopausal women, including improved lipid profiles and reductions in waist and hip circumferences, suggesting enhanced cardiovascular health and decreased abdominal fat. Although overall body composition metrics such as body weight and fat percentage remained unchanged, HIIT proved to be an effective, time-efficient exercise strategy.

The program also influenced hormonal levels, with increases in TSH, cortisol, and free T4, indicating activation of the thyroid and adrenal axes, although these changes remained within normal limits. Bone turnover markers showed reductions in Bone-ALP, calcium, phosphorus, osteocalcin, and CTX, suggesting alterations in bone metabolism.

Despite not achieving optimal changes in body composition, the HIIT model is a viable alternative for overweight and obese postmenopausal women who have limited exercise time. It effectively addresses waist and hip circumference, improves lipid profiles, and positively affects hormonal levels while maintaining bone health. Future research should focus on long-term effects, advanced body composition assessments, and dietary interventions.

Ethics

Ethics Committee Approval: This study was approved by the Marmara University Faculty of Medicine Ethics Committee (approval number: 09.2017.545, date: 01.06.2018).

Informed Consent: The participants provided written informed consent.

Footnotes

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

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Lactate Levels in Diabetic Ketoacidosis: Is There an Association Between the Severity of Acidosis and Length of Hospital Stay with Elevated Lactate Levels?

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ABSTRACT

Introduction: This study aimed to investigate the prevalence of lactic acidosis, its effect on the duration of intensive care unit (ICU) stay and hospital stay, and other factors affecting morbidity in patients with diabetic ketoacidosis (DKA).

Methods: We reviewed the records of 56 patients, including 26 (46.4%) girls and 30 (53.6%) boys, under 18 years of age, diagnosed as DKA. The cut-off value for elevated lactate levels was set at ≥2 mmol/L. The length of hospital stay, ICU stay, and mortality rate were recorded.

Results: There was no statistically significant correlation between length of hospital and ICU stay with lactate levels. In addition, no statistically significant relationship was found between the time of transition to subcutaneous therapy and lactate. There was a statistically significant positive correlation between lactate level, respiration rate, glucose level, and pediatric risk of mortality III score.

Conclusion: Lactic acidosis is common in pediatric patients with DKA. Although lactate levels were reported to be a significant independent predictor of morbidity and mortality in adult ICU patients, no effect was found on the length of hospital stay, ICU stay, and the time to transition to subcutaneous therapy with lactate levels in pediatric DKA patients.

Keywords: Type 1 diabetes, lactate, PRISM III score, lactic acidosis

Introduction

Diabetic ketoacidosis (DKA) is the most frequent acute complication of type 1 diabetes and the leading cause of diabetes-related fatalities (1,2). Ketoacidosis is a pediatric emergency, and approximately 15-67% of children with diabetes present with ketoacidosis upon diagnosis (2). Although the incidence of ketoacidosis-related mortality is reported to be 0.15-0.31% in Western countries, it is as high as 6-24% in developing countries (2,3). The factors that can influence mortality and morbidity in critically ill patients during ketoacidosis treatment should be recognized. The lactate level is increasingly being used as a predictor of illness severity and prognosis in critical condition. In the adult intensive care unit (ICU), high lactate levels are major independent predictors of mortality (4). According to the 2018 guidelines of the International Society of Pediatric and Adolescent Diabetes (ISPAD), while hyperglycemic hyperosmolar conditions were more prevalent, lactic acidosis could also occur in DKA cases. In DKA, the anion gap is usually between 20 and 30 mmol/L, with anion gaps greater than 35 mmol/L suggesting the presence of concomitant lactic acidosis (5). Increased lactate levels are common in patients with diabetes and are thought to be caused by increased anaerobic glycolysis due to tissue hypoperfusion and hypoxemia (6,7). However, its role in DKA is not well-defined. Our study aimed to investigate the prevalence of lactic acidosis, its effect on the duration of intensive care and hospital stay, and other factors affecting morbidity in patients with DKA.

Methods

A total of 56 patients with DKA aged 35-210 months, who were admitted to University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital between May 2019 and December 2022, were included in the study. According to the ISPAD 2018 guidelines, DKA is characterized by hyperglycemia (blood glucose >11 mmol/L or ~200 mg/dL), venous pH <7.3, serum bicarbonate <15 mmol/L, ketonemia (blood ß-hydroxybutyrate ≥3 mmol/L), or moderate to severe ketonuria (5). Patients who were referred to another center after the start of treatment and those who were referred to another center during treatment were excluded from the study.

Venous blood gas samples were obtained from all patients within 1 hour of admission to the emergency room. Patients were categorized into

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three groups according to their venous blood pH value and bicarbonate (HCO_3) levels: mild (pH <7.30, HCO_3 <15 mmol/L), moderate (pH <7.20, HCO_3 <10 mmol/L), and severe (pH <7.10, HCO_3 <5 mmol/L) ketoacidosis groups (5). The following information was obtained retrospectively from patient files: age at admission, gender, body mass index, age of diabetes diagnosis, length of hospital stay, Glasgow Coma Score, respiration rate, heart rate, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP). For patients who were followed up at the ICU, the length of ICU stay and pediatric risk of mortality III (PRISM III) score were evaluated (8). The PRISM III score calculation included 17 parameters; SBP, heart rate, temperature, mental status, pupillary response, acidosis, pH, pCO_2, total CO_2, pO_2, glucose, serum potassium, creatinine, blood urea nitrogen, total white blood cell count, platelet count, prothrombin time, and activated partial thromboplastin time.

Laboratory results were used to obtain data on glucose, blood pH, sodium, potassium, calcium, bicarbonate, anion gap, lactate in blood gas, pO_2 and pCO_2 in venous blood gas, leukocyte count, hemoglobin, platelets, C-reactive protein, glycosylated hemoglobin A1c (HbA1c) at diagnosis, C-peptide, urea, creatinine, and urinary ketone values. The length of hospital stay, length of ICU stay, and mortality rate were recorded. Each patients assessment included only one episode of ketoacidosis. Patients with heart failure, hepatic insufficiency, or history of drug use (metformin, acetaminophen and acetylsalicylic acid) that could cause lactic acidosis were excluded from the study. Although different studies have suggested different normal serum lactate levels, the cut-off value for elevated lactate levels was set at ≥2 mM in the present study (4,9). The relationship between the degree of acidosis, high lactate levels, and C-peptide levels and ICU and hospital stays was investigated.

The study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (2022/514/218/16, date: 28.01.2022).

Statistical Analysis

The IBM Statistical Package for the Social Sciences Statistics Standard Concurrent User v. 26 (IBM Corp., Armonk, New York, USA) software was used for data analysis. Descriptive statistics were presented as number of units (n), percentage (%), mean ± standard deviation, median, minimum, and maximum values. The Shapiro-Wilk test was used to assess the standard distribution hypothesis of numerical variables, whereas the Levene's test was used to test group homogeneity. The independent samples t-test or the Mann-Whitney U test was applied to compare numerical variables between the lactate <2 and lactate ≥2 groups. The Kruskal-Wallis test was used to compare the length of hospital stay among the pH groups, with multiple comparisons conducted using the Dunn-Bonferroni test. The relationship between numerical variables was examined using Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

Results

The study files of 56 patients reviewed, including 26 (46.4%) girls and 30 (53.6%) boys. The median age of the participants was 123.5 months (range, 35-210 months). Forty (71.4%) patients were newly diagnosed, whereas sixteen (28.6%) were previously diagnosed. The age at diagnosis varied from 35 to 209 months, with a median age of 103.5 months. Thirty-four patients (60.7%) were followed up in the ICU, and the median length of stay was 2 days. The descriptive features of the patients are summarized in Table 1.

Table 1. Descriptive characteristics of patients (n=56)

Variables	Statistics
Age, (months)	
$\bar{X} \pm$ SD	123.75±49.06
Median (minimum-maximum)	123.5 (35.0-210.0)
Sex, n (%)	
Girls	26 (46.4)
Boys	30 (53.6)
Diagnosis, n (%)	
Newly diagnosed	40 (71.4)
Previously diagnosed	16 (28.6)
Age at diagnosis (months)	
$\bar{X} \pm$ SD	106.98±46.03
Median (minimum-maximum)	103.5 (35.0-209.0)
Body mass index (kg/m²)	
$\bar{X}\pm$ SD	17.48±3.48
Median (minimum-maximum)	16.55 (10.8-27.4)
Admission to the ICU, n (%)	
Yes	34 (60.7)
No	22 (39.3)
Length of ICU stay (days)	
$\bar{X} \pm$ SD	2.52±2.13
Median (minimum-maximum)	2.0 (1.0-14.0)
When were normal lactate levels achieved? (hours)	
$\bar{X}\pm$ SD	7.01±5.66
Median (minimum-maximum)	4.0 (1.0-24.0)
Lactate (mM)	
$\bar{X} \pm$ SD	2.84±1.16
Median (minimum-maximum)	2.5 (1.2-6.1)
Glucose (mg/dL)	
$\bar{X} \pm$ SD	518.01±126.41
Median (minimum-maximum)	497.0 (268.0-897.0)
pH	
$\bar{X} \pm$ SD	7.05±0.12
Median (minimum-maximum)	7.07 (6.8-7.3)
GFR (mL/min/1.73 m²)	
$\bar{X} \pm$ SD	115.17±24.64
Median (minimum-maximum)	112.50 (74.5-197.0)
Creatinine (mg/dL)	
$\bar{X} \pm$ SD	0.77±0.21
Median (minimum-maximum)	0.720 (0.41-1.43)
HCO_3 (bicarbonate) (mmol/L)	
$\bar{X} \pm$ SD	9.52±3.81
Median (minimum-maximum)	9.0 (4.0-24.0)
Mean arterial pressure (mmHg)	
$\bar{X} \pm$ SD	84.44±12.64
Median (minimum-maximum)	87.0 (53.0-111.0)

SD: Standard deviation, min: Minute, ICU: Intensive care unit, GFR: Glomerular filtration ratio

In terms of acidosis severity, 7 (12.5%) patients were classified into the mild group, 18 (32.1%) in the moderate group, and 31 (55.4%) in the severe group. We found a statistically significant difference between these groups in terms of acidosis severity and length of hospital stay. The total length of hospital stay was significantly longer in the severe acidosis group than in the moderate and mild acidosis groups. The relationships between the mild, moderate, and severe acidosis groups and the total length of hospital stay are summarized in Table 2.

We found no difference among 3 groups in terms of lactate level and cardiac apex beat, SBP, DBP, and MBP (rho: 0.115, p=0.399; rho: 0.019, p=0.892; rho: 0.027, p=0.844; and rho: -0.023, p=0864, respectively), and we found a positive correlation between the lactate level and respiratory rate (rho: 0.307; p=0.022).

No significant correlation was found among the 3 groups regarding the time to transition to subcutaneous therapy and lactate level (rho: 0.141; p=0.309).

There was no correlation between lactate and heart rate, SBP, DBP, MBP, length of hospital stay, length of ICU stay, time of transition to subcutaneous therapy, or C-peptide level (Table 3). Lactate level was positively correlated with respiration rate, glucose level, and PRISM III score, and there was a negative correlation between lactate and pH.

There was no correlation between the time of transition to subcutaneous therapy and lactate level (rho: 0.141; p=0.309). No significant relationship was found between the PRISM III score and length of hospital stay (rho: 0.227; p=0.198), and the PRISM III score and length of ICU stay (rho: 0.112; p=0.528). A significant positive relationship between C-peptide levels and pH was found (rho: 0.384; p=0.006).

There was no statistical difference between the high and normal lactate groups based on age and gender (Table 4). The lactate ≥2 group had significantly higher glucose and creatinine levels. The lactate groups had statistically similar sodium, potassium and HbA1c values. The pH and bicarbonate values of the lactate ≥2 group were lower than the lactate <2 group. No significant difference was found between the groups in terms of $PaCO_2$ levels. The lactate ≥2 group had statistically higher anion gap values. We found no differences among the groups in SBP, DBP, time to transition to subcutaneous treatment, or C-peptide levels.

There was no correlation between length of stay and anion gap, glucose, sodium, potassium, and lactate (Table 5).

No comorbidities or deaths were recorded in our study group.

Table 2. A comparison of length of hospital stay based on the severity of acidosis

	Severity of acidosis			Test statistics	
	Mild, (n=7)	Moderate, (n=18)	Severe, (n=31)	H	p
LOHS (days)					
Median (minimum-maximum)	7 (4-9)[a]	7 (3-10)[a]	9 (3-21)[b]	10,137	0.006

H: Kruskal-Wallis test; superscripts ([a]) and ([b]) indicate groups with statistically significant differences. Groups with the same superscripts were statistically similar. LOHS: Length of hospital stay

Table 3. Correlations between lactate level and other variables

	Lactate	
	rho	p
Heart rate	0.115	0.399
Systolic blood pressure	0.019	0.892
Diastolic blood pressure	0.027	0.844
Respiration rate	**0.307**	**0.022**
Mean arterial pressure	-0.023	0.864
Length of hospital stay	-0.134	0.325
Length of ICU Stay	-0.089	0.616
Time from transition to subcutaneous treatment	0.141	0.309
Glucose	**0.301**	**0.024**
PRISM III score	**0.606**	**<0.001**
C-peptide levels	-0.116	0.426
pH	**-0.435**	**0.001**

Rho: Spearman correlation coefficient; bold values indicate statistical significance. ICU: Intensive care unit, PRISM III: Pediatric risk of mortality III

Discussion

The current study examined pediatric patients with DKA admitted to the emergency department. Our study aimed to identify the factors contributing to prolonged hospital stays and to determine the effect of lactic acid levels on transition to subcutaneous treatment and length of hospitalization. Lactate levels showed a statistically significant positive correlation with respiration rate, glucose levels, and PRISM III score, whereas a statistically significant negative correlation with pH was noted.

Studies involving non-diabetic patients reported that high lactate levels were associated with longer ICU stay and increased mortality in critically ill patients as well as in patients with sepsis who were admitted to the ICU for follow-up (10-12).

In their extensive retrospective study, Khosravani et al. (4) found that a lactate level of ≥2 mmol/L upon admission was an important predictor of mortality among adults admitted to ICUs. Kruse et al. (9) conducted a systematic review of 33 articles and determined that single lactate measurements at hospital admission were valuable for predicting adverse outcomes. They recommended close monitoring for patients with lactate levels ≥2.5 mM at admission. The study found an acceptable correlation between lactate levels in arterial and venous blood samples, suggesting that venous sampling is associated with minimal risk and inconvenience for patients. They reported a negative correlation between pH and lactate. However, a relationship was found between lactate levels and length of hospital stay (9).

In 2021, Masharani et al. (13) reported data from 79 adults hospitalized for DKA. Increased blood glucose levels and hydrogen ion concentrations were correlated with higher lactate levels. A decrease in the glomerular filtration rate was also related to a higher lactate (13). Because metformin therapy may increase lactate levels by decreasing renal clearance, no patients were treated with metformin in the present study.

James et al. (14) reported that lactic acidosis in patients may be due to sepsis or trauma in the absence of tissue hypoperfusion. The authors suggested that the activity of the muscle Na-K pump increases

Table 4. Comparisons based on lactate levels

	Lactate level		Test statistics	
	<2, (n=8)	**≥2, (n=48)**	**Test value**	**p-value**
Lactate level (mmol/L)	1.65 (0.25)	2.65 (1.48)	*z*=4.508	**<0.001**
Age (months)	134.2±57.6	122.0±47.9	*t*=0.650	0.518
Gender (girls/boys)	6/2	20/28	χ^2=3.063	0.127
Glucose (mg/dL)	419.7±83.4	534.3±125.4	*t*=2.484	**0.016**
Creatinine (mg/dL)	0.54 (0.24)	0.77 (0.29)	*z*=2.917	**0.002**
Sodium (mmol/L)	132.2±3.8	131.2±4.9	*t*=0.525	0.602
Potassium (mmol/L)	4.11±0.71	4.47±0.64	*t*=1.438	0.156
HbA1c (%)	12.56±1.82	12.93±1.99	*t*=0.498	0.620
pH	7.18±0.12	7.04±0.11	*t*=3.381	**0.001**
Bicarbonate (mmol/L)	14.05 (5.98)	8.25 (4.65)	*z*=2.369	**0.016**
$PaCO_2$ (mmHg)	26.37±11.47	23.82±7.32	*t*=0.836	0.407
Anion gap	19.1±5.1	23.1±4.9	*t*=2.072	**0.043**
Systolic blood pressure (mmHg)	110.0 (27.5)	110.0 (20.0)	*z*=0.285	0.792
Diastolic blood pressure (mmHg)	72.5 (28.7)	72.5 (20.0)	*z*=0.071	0.954
Time to transition to subcutaneous treatment (hour)	11.4 (3.1)	12.7 (1.7)	*z*=1.793	0.075
C-peptide level (ng/mL)	0.41 (0.71)	0.34 (0.25)	*z*=0.357	0.727

Data are expressed in mean ± standar deviation or median (interquartile range), *z*: Mann-Whitney U test, *t*: Independent samples t-test, χ^2: Chi-squared test, and bold p-values are statistically significant. HbA1c: Hemoglobin A1c

with increased epinephrine levels and thus causes increased lactate production (14). In patients with DKA, insulinopenia and stress may activate counterregulatory hormones and cause an increase in epinephrine levels (15). Bolli et al. (15) reported that increased epinephrine levels may increase the severity of ketoacidosis. Increased lactic acid levels in patients with sepsis and trauma are often associated with tissue hypoperfusion, whereas in patients with DKA, they are associated with increased levels of counterregulatory hormones. This explains why lactic acidosis is not an important indicator of mortality in patients with DKA, as it is in those with sepsis and trauma.

It was reported in relevant studies with adult patients that lactic acidosis was prevalent in DKA patients and that elevated lactate levels were not correlated with the length of ICU stay and mortality (6,13,16). Only a few studies have investigated elevated lactate levels associated with DKA in the pediatric age group. Cully et al. (17) evaluated 92 pediatric patients and reported that lactate levels were >2.5 mmol in 63.7% of the patients and that lactate levels were associated with glucose levels during admission; these findings were similar to those of adult studies. A study involving pediatric cases monitored in the ICU for severe ketoacidosis found a negative relationship between lactate levels and the recovery time from DKA (18). Nevertheless, lactate levels were positively correlated with glucose levels.

Elevated lactate levels were a common finding in our study, and the lactate level was found to be ≥2 mmol in 85.7% of the patients. The findings of our study are consistent with those of the current literature. There was no correlation between lactate levels, transition to subcutaneous treatment, and length of hospital stay.

Table 5. Correlation between length of hospital stay and anion gap, glucose, sodium, and potassium levels

	Length of hospital stay	
	rho	**p**
Anion gap	-0.054	0.692
Glucose	-0.088	0.518
Sodium	0.035	0.796
Potassium	-0.242	0.073
Lactate	-0.134	0.325

rho: Spearman's correlation coefficient

Furthermore, there was no obvious difference in lactic acid levels, transition to subcutaneous therapy, or length of hospital stay between the groups. Patients with severe ketoacidosis had longer hospital stays than those with mild or moderate ketoacidosis. This was attributed to the fact that patients with severe ketoacidosis were primarily monitored in intensive care, which delayed diabetes education. Although higher lactate levels were associated with poorer clinical outcomes in patients with trauma, sepsis, and burns, lactate levels were not associated with increased morbidity and mortality in patients hospitalized due to DKA (19-21). Similarly, elevated lactate levels did not increase morbidity and mortality in the current study.

Inadequate tissue perfusion due to volume depletion and relative hypoxemia are the main causes of lactate elevation in patients with DKA. Despite higher blood glucose levels in patients with DKA, tissue glucose secretion is insufficient because of insulinopenia. This causes a hypoglycemic response in the tissues, especially brain tissue. As a result, lactate production can meet the brain's need for fuel, which is known as

"alternative fuel hypothesis" (7). Hyperlactatemia is frequent in patients with DKA and is not linked to unfavorable outcomes. The results suggest that a thorough assessment and empirical treatment of sepsis solely based on elevated lactate levels might be unnecessary.

No deaths due to DKA or related complications were recorded. Only one patient was intubated because of unconsciousness upon admission and required dialysis because of a gradual increase in creatinine levels. A study in Türkiye reported that only 1 patient was lost due to sepsis and multiorgan failure among 119 patients with DKA who were followed up in the pediatric ICU. In the relevant study, the median length of ICU stay was 2 days, and the median length of hospital stay was reported 8 days (22).

Study Limitations

The present study has certain limitations. Clinical and laboratory data were retrospectively recorded in patient files. Due to the limited sample size, studies with larger sample sizes are required to ascertain the clinical importance of lactic acidosis in pediatric patients with DKA in emergency services.

Conclusion

Lactic acidosis is common in pediatric patients with DKA. Nevertheless, its clinical significance remains unclear. Thus, serum lactate levels alone should not be used as a predictor of outcomes in pediatric DKA. Lactic acid levels are expected to return to normal in patients with DKA who receive appropriate intravenous fluid and insulin replacement. In patients with persistently high lactic acid levels despite improvement in hyperglycemia, we recommend that patients be further evaluated for underlying diseases.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (2022/514/218/16, date: 28.01.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - E.S., U.Y.; Concept - E.S., F.H.E.; Design - E.S., U.Y., M.T.K.; Data Collection or Processing - E.S., U.Y., M.T.K.; Analysis or Interpretation - M.T.K., Y.A., F.H.E.; G.E.; Literature Search - E.S., Y.A.; Writing - E.S.

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Comparison of the Effectiveness of Blinded Versus Ultrasound-Guided Trigger Point Injections into the Trapezius Muscle in Patients with Fibromyalgia

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ABSTRACT

Introduction: The primary objectives of treating fibromyalgia syndrome (FMS), which frequently coexists with myofascial pain syndrome (MPS), are to deactivate trigger points, alleviate pain, and remove factors that exacerbate the condition. Recently, the use of ultrasound (US) has been advocated to reduce potential complications during trigger point injections (TPI) and to ensure a more effective treatment administration. This study aimed to compare the effectiveness of blinded versus US-guided TPI into the trapezius muscle in patients with FMS and associated MPS.

Methods: A total of 75 patients with FMS and trapezius muscle trigger points indicative of MPS participated in this study. They were randomly assigned to one of two groups: the US-guided trigger point group and the blinded trigger point group. Both groups followed the same home exercise regimen, which included stretching and posture exercises targeting the trapezius and pectoral muscles. The effectiveness of the treatments was evaluated one month after treatment. The assessment tools included the Fibromyalgia Impact Questionnaire for function, the visual analog scale for pain, the Beck Anxiety Inventory for anxiety, and the Neck Disability Questionnaire for neck disability.

Results: Data from 60 patients were included in the final analysis. No statistically significant differences were found between the demographic variables of the two groups ($p>0.05$). A comparison of US-guided and blinded TPI revealed a significant difference in neck disability ($p=0.041$). Both groups showed significant improvements in all evaluated parameters from pre-treatment to post-treatment ($p<0.05$).

Conclusion: US-guided TPI positively impacted pain, function, anxiety, and neck pain in patients with FMS and associated MPS. This method can be recommended in clinical settings to help alleviate the symptoms of both conditions.

Keywords: Fibromyalgia, injection, myofascial pain syndrome, trigger point

Introduction

Fibromyalgia syndrome (FMS) is characterized by chronic, widespread musculoskeletal pain that is often accompanied by other symptoms, such as fatigue, sleep disturbances, and mood disorders. It is estimated that 2-8% of the world population will be affected by FMS (1). Although FMS can be observed in all races at any age and sex, it is most commonly observed in patients aged 40-60 years and female patients (2). The pathogenesis of FMS is still not fully explained (3). Central sensitization plays a role in FMS, chronic fatigue syndrome, functional dyspepsia, interstitial cystitis, irritable bowel syndrome, temporomandibular joint dysfunction, myofascial pain syndrome (MPS), posttraumatic stress disorder, and restless legs syndrome (3,4). Pain is associated with disease severity, decreased functional level, and FMS in individuals with FMS. Therefore, it is an important symptom that may affect physical functionality (5).

MAS is a regional pain disorder that affects all age groups and manifests itself with symptoms and signs, such as pain, spasm, and limitation of movement, characterized by hypersensitive points in muscles or fascia called trigger points (6). Although the exact prevalence of MAS in the general population is not clearly stated in the available literature, some studies have revealed that MAS accounts for 30-85% of musculoskeletal pain cases (7).

Neck and upper back pain is the most common complaint of MAS because the trapezius muscle is affected. The main goal of this approach is to

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achieve normal muscle length, function, and strength by eliminating muscle tension and alleviating chronic pain (8). Chronic pain causes insomnia, anxiety, and depression and may be a multidimensional problem by causing a comorbid or secondary decrease in activity (9).

The goal of treating MAS is to deactivate trigger points, alleviate pain, and eliminate factors that exacerbate the condition. Several treatment modalities are available for managing MAS. Trigger point injections (TPI), which have been used for years to treat musculoskeletal pain, are the most common treatment for refractory MAS (10,11). Trigger points are usually palpated during physical examination before injection. In obese patients, palpation of trigger points is challenging and sometimes impossible. It is difficult to know whether the needle is properly inserted into the muscle tissue in these patients. This may lead to an increase in complications, such as pneumothorax or injection into adipose tissue, when performing TPI in the posterolateral neck and thoracic spine muscles (12). Recently, some authors have recommended the use of diagnostic ultrasound (US) to reduce potential complications during TPI and to enhance injection effectiveness (12-14).

This study aimed to compare the effectiveness of blinded versus US-guided TPI into the trapezius muscle in individuals with FMS.

Methods

The sample size and power calculation for the study were determined using G*Power version 3.1.9.4. In the power analysis based on the results of the comparison of the difference between the visual analog scale (VAS) score averages in the study of Ateş and Çoğalgil (15) with the risk of α=0.05, 1-α=0.80 accuracy rate condition, and the effect size 0.75 actualpower: 0.80, it was concluded that a minimum of 30 people should participate in each group. Randomization was performed in 75 patients to reduce possible sample loss.

The study included 75 patients aged 20-60 years who were admitted to the Physical Medicine and Rehabilitation Outpatient Clinic of Elazığ Medical Hospital with FMS meeting the 2013 ACR criteria and cervical chronic MAS meeting the diagnostic criteria of Travell and Simons. Fifteen patients who met the exclusion criteria were excluded from the study. The study was continued for 60 patients. The randomization of the groups was performed by simple randomization using the website www.random.org. Participants were included in the groups according to the randomization list. Participants were explained that they would receive one of two different forms of TPI, but they were blinded to the study hypotheses. The first group (n=30) received MAS injection under US-guidance. The second group (n=30) received a blinded MAS injection. Both groups followed an identical home exercise regimen, which included stretching and posture exercises for the upper trapezius and pectoral muscles, administered simultaneously. Patients were reassessed 1 month after treatment to evaluate the effectiveness of the intervention.

Patients aged 20-60 years who met the 2013 ACR criteria, were diagnosed with FMS and cervical chronic MAS according to Travel and Simons criteria, had a palpated tense band in the upper trapezius muscle, and at least 1 active trigger point were included in the study. Patients with a diagnosis of cervical radiculopathy, myelopathy, local or systemic infection, treatment for MAS in the last 3 months, symptom duration less than 3 months, pregnancy status, acute or chronic disease that would cause clinical confusion at the time of the study (malignancy, fracture, organ failure vs.), uncompensated cardiovascular disease, history of inflammatory disease, history of bleeding diathesis, anticoagulant use, and cognitive inability to communicate were excluded.

Approval for our study was obtained from the Fırat University Non-Interventional Research Ethics Committee (approval number: 2024/03-10, date: 13.02.2024), and all patients were informed verbally and in writing about the study, and a consent form was signed.

Outcome Measurements

All patients were evaluated by the same investigator before treatment, and demographic information was obtained. Post-treatment controls were evaluated by an expert investigator who was blinded to the study.

The pain levels of the patients in the last week were questioned using a 0-10 cm long VAS. “0” indicated that the patient had no pain, and “10” indicated that the patient’s pain was unbearably severe (16).

Functional evaluation of the patients was performed using the Fibromyalgia Impact Questionnaire (FIQ). The FIQ is a 10-item scale that evaluates the health status and physical function of patients with FMS. A Turkish validity and reliability study was conducted by Sarmer et al. (17). High scores indicate low functionality.

The Beck Anxiety Scale (Beck-A) was used to determine the anxiety level of the patients (18). The Likert scale comprises 21 items describing anxiety symptoms. Each item was graded as none-mild-moderate-severe or scored between 0 and 3. Total score <10 indicates minimal or none, 10-18 mild-moderate, 19-29 moderate-severe, 30-63 severe anxiety (18).

The Neck Disability Questionnaire (NDQ) was used to assess the effect of neck pain on daily life (19). The questionnaire comprises 10 questions probing the effect of neck pain on pain sensitivity, personal care, weight lifting, reading, headaches, concentration, work/study, driving, sleep, and social activities. Patients were asked to choose only one of the 6 answer options for each question, considering the last month. Scoring was performed between 0 and 5 for each question. For the 10 questions, a score between 0 and 50 was obtained by summing the scores of the 10 selected options. The classification of limitations according to the NDQ score was as follows: 0-4: no limitation, 5-14: mild limitation, 15-24: moderate limitation, 25-34: severe limitation, >34: totally limited.

Intervention

The trigger points of all cases were determined and marked with a pencil at the beginning of the procedure. The skin was then cleaned with a suitable antiseptic solution, and a sterile, 25 G, 1.5-inch dental-tip needle was used. All patients were injected with 5 mL of 2% lidocaine + 5 mL of 0.9% NaCl. During injection in the first group; the linear probe (PLT-704SBT, 7.5 MHz) of the US device (Toshiba Aplio 300, Japan) was kept parallel to the trapezoidal fibers on the marked trigger point, and the dental-tipped needle was directed to the targeted point in the plane with real-time imaging (12). While injecting the second group; the needle was directed to the most sensitive point and advanced until it reached the trigger point. When the trigger point was touched, it was confirmed

that we were within the trigger point by feeling tenderness and pain not only in the local area but also in the reflection area and by observing the local twitch response or contraction of the band containing the trigger point. After negative aspiration, 0.5 cc of the solution prepared at each trigger point was injected intramuscularly.

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 22.0 for Microsoft Windows. To assess whether the data followed a normal distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. The data were then analyzed using either parametric or non-parametric statistical methods, as appropriate. Descriptive statistics are reported as numbers, percentages, and as minimum, maximum, mean ± standard deviation. Categorical variables were examined using the Pearson's chi-squared test, whereas continuous variables were assessed using the Independent t-test and Mann-Whitney U test. For dependent group comparisons, the Wilcoxon test was used to non-parametric data, and the Paired Sample t-test was used for parametric data. A p-value 0.05 was considered statistically significant.

Results

The demographic characteristics of the patients are presented in Table 1. There were no statistically significant differences in demographic variables among the three groups concerning demographic variables ($p>0.05$). Figure 1 illustrates the study design and flow chart. The study included 60 female patients. Group 1 consisted of patients receiving US-guided injections, while group 2 consisted of those receiving blinded injections. The mean number of active trigger points detected and injected in group 1 was 3.30±1.20, while the mean number of active trigger points detected and injected in group 2 was 3±1.28. There was no significant difference in the number of injections between the two groups ($p=0.348$). A summary of the pre- and posttreatment comparisons between the two groups is presented in Table 2, revealing a significant difference only in the NDQ ($p=0.041$). Table 3 presents a comparison of the groups before and after treatment, showing statistically significant differences in the parameters assessed post-treatment in both groups ($p<0.05$). Table 4 summarizes the subgroup ratios for VAS, NDQ, and Beck-A in both groups, where no significant differences were observed in the analyzed parameters.

Discussion

This study aimed to compare US-guided and blinded TPIs. The results of the study demonstrated that there was no significant difference between US-guided and blinded applications in pain, anxiety, and FIQ; a significant difference was obtained only in the NDQ. Although no statistically significant difference was observed, the US-guided application was found to provide more improvement in pain, anxiety, and FIQ. In addition, significant differences in the evaluated parameters were observed between both groups. These results suggest that US-guided injection is important in clinics because it can provide better clinical outcomes.

Significant differences were observed in pain, neck disability, FIQ, and anxiety after the interventions in both groups. Chronic widespread pain is the main symptom of FMS. Chronic and recurrent pain can cause loss of function and become a socioeconomic problem with its financial burden, as well as affecting the whole life of the individual (20). Among diseases that cause chronic widespread pain and disability, MAS is an important pain syndrome that is generally ignored by physicians. Timely detection and treatment of trigger points can prevent the progression of MAS (21). One treatment method is local anesthetic injection. This method provides both local pain control and blood flow stimulation

Table 1. Demographic characteristics of participants in groups 1 and 2

Parameters (mean ± SD)		Group 1, (n=30)	Group 2, (n=30)	p
Age (years)		44.03±11.14	45.40±9.72	0.609*
Weight (kg)		67.70±10.59	70.50±11.23	0.325**
Height (cm)		160.70±5.52	160.80±6.39	0.949**
BMI (kg/cm^2)		26.33±4.70	27.38±4.89	0.145**
Education level	Primary school	7 (23.3%)	1 (3.3%)	0.145***
	Middle school	13 (43.3%)	18 (60%)	
	High school	5 (8.3%)	6 (20%)	
	University	5 (16.7%)	5 (16.7%)	
Marital status	Married	23 (76.7%)	21 (70%)	0.559***
	Single	7 (23.3%)	9 (30%)	
Menopause	Yes	10 (33.3%)	12 (40%)	0.592***
	No	20 (66.7%)	18 (60%)	
Smoking	No	6 (20%)	7 (23.3%)	0.754***
	Former smoker	24 (80%)	23 (76.7%)	
Working status	No	24 (80%)	27 (90%)	0.278***
	Yes	6 (20%)	3 (10%)	
Number of trigger points		3.30±1.20	3±1.28	0.348*

SD: Standard deviation, BMI: Body mass index, *: Mann-Whitney U test, **: Independent t-test, ***: Pearson's chi-squared test

to ischemic tissues. Prilocaine injections can also provide symptom-free periods of 2 weeks to 3 months (15). TPI is considered the gold standard in trigger point treatment because it is a rapid and effective method for pain relief. The results of this study demonstrated that TPI was effective in terms of clinical parameters. Therefore, TPI, with or without US guidance, should be applied together with other physical therapy methods, as described in this study (22). It is known that neck pain is effective in reducing the psychological, social, and physical status of patients with FMS (23). Improvements in the levels of neck disability, functional level, and anxiety may stem from the decrease in pain observed in this study.

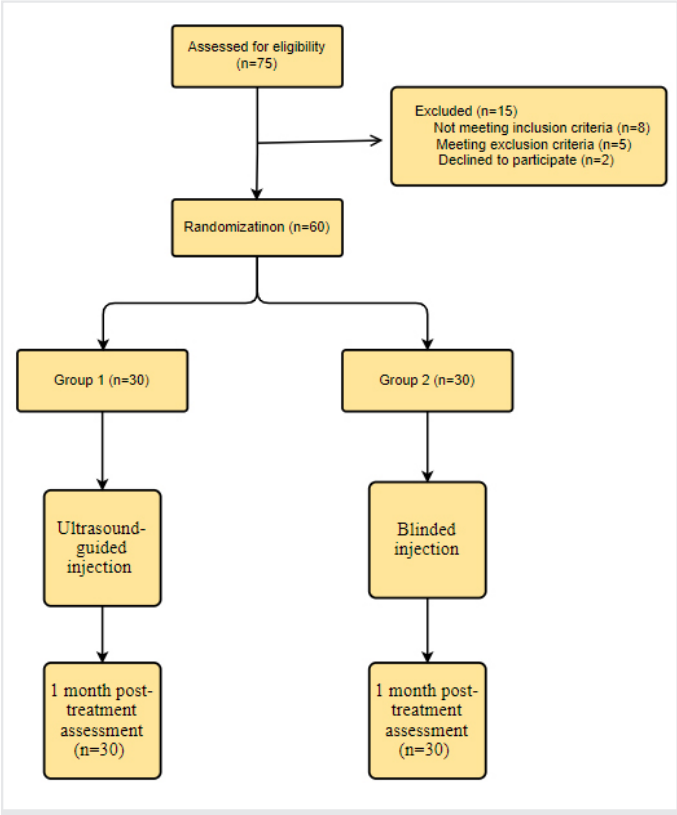

Figure 1. Study flow chart

Although there was no significant difference between US-guided and blinded injection in many parameters, it was observed that US-guided injection provided more improvement when the changes in the groups were analyzed in our study. The small sample size may be a reason for not obtaining a statistically significant differences. A significant difference could be observed with a larger sample. Injections into the upper trapezius muscle, which is only a superficial muscle, may be effective for similar improvement in both groups. Deep injections are recognized as more effective than superficial injections, and using US guidance can help reduce the risk of complications associated with blind injections, such as pneumothorax, air embolism, accidental intrathecal injection, peripheral nerve injuries, and muscle injuries (24). In a review study including US-guided applications, it was reported that all applications resulted in zero or minimal side effects. Therefore, US provides a significant advantage for deep injections (25). However, similar side effects are less common in superficial applications. Therefore, the results of this study suggest that the use of US in superficial injections may provide more successful results in terms of clinical parameters. However, blinded treatment is also effective. In a study conducted by Kang et al. (26), similar to our study, US-guided TPI was demonstrated to be a more useful method than blind injection. Kang et al. (26) evaluated the effects of 4 weeks of treatment in this study; we evaluated the acute effects in this study. The lack of long-term results in our study may be a deficiency, but according to the authors' knowledge, no study has evaluated the acute effects of TPI application in the literature. The proposed method is important in terms of evaluating the gains obtained immediately after application. Ultrasonography has the potential to be a diagnostic aid at the bedside to help clinicians make an accurate diagnosis, improve patient experience during examination, and avoid unnecessary treatments that may reduce the risk of iatrogenic damage.

Table 2. Comparison of the pre- and posttreatment values of pain, function, disability, and anxiety between groups 1 and 2

Parameters	Pre-treatment			Post-treatment		
	Group 1, (n=30)	Group 2, (n=30)	p	Group 1, (n=30)	Group 2, (n=30)	p
VAS	8.00±1.55	7.40±1.56	0.136*	6.40±1.69	6.76±1.56	0.474*
FIQ	64.38±6.99	62.18±8.88	0.292**	58.81±6.43	59.85±7.09	0.555**
NDQ	31.23±11.30	28.43±10.54	0.325**	20.33±8.20	26.20±10.47	**0.041***
Beck-A	27.60±12.38	28.80±12.44	0.709**	24.86±10.66	26.36±11.33	0.610*

VAS: Visual analog scale, FIQ: Fibromyalgia Impact Questionnaire, NDQ: Neck Disability Questionnaire, Beck- A: Beck Anxiety Scale, *: Mann-Whitney U test, **: Independent t-test

Table 3. Comparison of parameters before and after treatment in groups 1 and 2

Parameters	Group 1			Group 2		
	Pre-treatment	Post-treatment	p	Pre-treatment	Post-treatment	p
VAS	8.00±1.55	6.40±1.69	**<0.001***	7.40±1.56	6.76±1.56	**0.014***
FIQ	64.38±6.99	58.81±6.43	**<0.001****	62.18±8.88	59.85±7.09	**0.006***
NDQ	31.23±11.30	20.33±8.20	**<0.001***	28.43±10.54	26.20±10.47	**0.010***
Beck-A	27.60±12.38	24.86±10.66	**0.001***	28.80±12.44	26.36±11.33	**0.002***

VAS: Visual analog scale, FIQ: Fibromyalgia Impact Questionnaire, NDQ: Neck Disability Questionnaire, Beck-A: Beck Anxiety Scale, *: Wilcoxon test, **: Paired sample t-test

Table 4. Subgroup comparison of pain, neck disability, and anxiety in the two groups

Parameters		Pre-treatment			Post-treatment		
		Group 1, (n=30)	Group 2, (n=30)	p*	Group 1, (n=30)	Group 2, (n=30)	p*
VAS	Mild			0.317	1 (3.3%)		0.559
	Moderate	4 (13.3%)	7 (23.3%)		14 (46.7%)	13 (43.3%)	
	Vigorous	26 (86.7%)	23 (76.7%)		15 (50%)	17 (56.7%)	
NDQ	Mild	1 (3.3%)	3 (10%)	0.433	10 (33.3%)	5 (16.7%)	0.223
	Moderate	8 (26.7%)	8 (26.7%)		10 (33.3%)	10 (33.3%)	
	Vigorous	9 (30%)	12 (40%)		9 (30%)	10 (33.3%)	
	Completely disabled	12 (40%)	7 (23.3%)		1 (3.3%)	5 (16.7%)	
Beck-A	No/minimal	2 (6.7%)	3 (10%)	0.342	2 (6.7%)	4 (13.3%)	0.553
	Mild/moderate	8 (26.7%)	4 (13.3%)		8 (26.7%)	4 (13.3%)	
	Moderate/vigorous	5 (16.7%)	10 (33.3%)		11 (36.7%)	12 (40%)	
	Vigorous	15 (50%)	13 (43.3%)		9 (30%)	10 (33.3%)	

VAS: Visual analog scale, NDQ: Neck Disability Questionnaire, Beck-A: Beck Anxiety Scale, *: Pearson's chi-squared test

Trigger point detection is generally thought to require palpation, but patient tension or startle during palpation may adversely affect the result. Another consideration is the size of the trigger point. For example, trigger points in the upper fibers of the trapezius can be as small as 0.16 ± 0.11 cm^2 and this may cause difficulty in detecting abnormalities in the tissue under the fingers of the palpator (1,27). Therefore, the use of the US may provide more accurate and clear information. This is encouraging because US is a more objective method for diagnosing trigger points. Although visualizing individual trigger points can be challenging because of their small size, some experts recommend using US to ensure accurate needle placement into muscle tissue, avoiding fat or other non-muscle structures during TPI (12).

A significant difference in neck disability between the groups was obtained from this study. Rayalam et al. (28) reported studies on TPI with US guidance and a blinded method. At the end of 4 weeks, no significant difference was observed in manual muscle testing and range of motion, but a significant difference was observed in pain, neck disability, and shoulder disability. In this study, the neck disability level was evaluated using a questionnaire. In this questionnaire, we evaluated neck pain and difficulties in activities of daily living. Although no significant difference was obtained in the pain levels of the patients who participated in our study, the fact that a significant difference was obtained in the level of neck disability may be due to the fact that the patients could use their neck more comfortably in daily life.

Study Limitations

This study has some limitations. The lack of deep tissue injection and not determining possible side effects are limitations for this study. In addition, the small sample size is a limitation of this study.

Conclusion

In our study examining the effects of US-guided and blinded TPI on clinical parameters, we found that both methods were effective for pain, disability, anxiety, and FIQ. Our study is important because it is the first to investigate the acute effects of TPI on clinical symptoms. However, we conclude that US-guided treatment is more effective at the level of neck disability. The development of US technology has significantly improved the quality of soft tissue and muscle scans. The use of US in the TPI technique, real-time imaging of trigger points, and visualization of surrounding tissues or important structures can lead to more successful results. Safety is an important aspect for patients and should not be overlooked. Future research could focus on establishing more objective diagnostic criteria for trigger points through the use of US imaging.

Ethics

Ethics Committee Approval: Approval for our study was obtained from the Fırat University Non-Interventional Research Ethics Committee (approval number: 2024/03-10, date: 13.02.2024).

Informed Consent: All patients were informed verbally and in writing about the study, and a consent form was signed.

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.Ş.E.; Concept - M.Ş.E.; Design - M.Ş.E.; Data Collection or Processing - M.Ş.E.; Analysis or Interpretation - M.Ş.E., S.B.Y.; Literature Search - M.Ş.E., S.B.Y.; Writing - M.Ş.E., S.B.Y.

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

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Impact of COVID-19 on Hematologic Disorders: Clinical Insights and Challenges

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ABSTRACT

Introduction: Early studies indicated that patients with cancer had substantially elevated risks of undesirable coronavirus disease-2019 (COVID-19) outcomes, especially higher mortality rates. There are several reports that not all hematological malignancies have a fatality risk. We aim to contribute to the literature by evaluating patients diagnosed with COVID-19 during the pandemic in the field of hematology.

Methods: This single-center, retrospective, cohort study included adult patients (aged ≥18 years) with COVID-19 who had a World Health Organization-defined hematological malignancy or non-neoplastic hematologic disorder and were admitted to İstanbul University, İstanbul Faculty of Medicine between March 2020 and May 2023. The primary outcome was mortality. We also evaluated the outcomes according to the type of hematologic disorder, age, disease status at the time of COVID-19 diagnosis, severity of COVID-19, comorbidities, and vaccination status. Treatment modalities were also collected. Statistical analysis was performed using StataMP 17.

Results: We enrolled 285 patients. The median age was 57 years, and male predominance (55%). Fifty-one (17.89%) patients died. Patients aged ≥65 years were at increased risk of death ($p<0.001$). The mortality rate was significantly higher in patients with lymphoid malignancy, especially those with chronic lymphocytic leukemia (CLL) ($p<0.001$). In the multivariate analysis, the need for anakinra administration, intubation, and COVID-19 progression increased the risk of death.

Conclusion: Hematologic patients are susceptible to COVID-19. Elderly individuals with active hematological disease are particularly at risk. Patients with CLL should be closely monitored. The need for anakinra, intubation, and COVID-19 progression increased the risk of death.

Keywords: Chronic lymphocytic leukemia, hematological malignancy, SARS-CoV-2

Introduction

Numerous challenges were encountered during the first coronavirus disease-2019 (COVID-19) wave in various populations. Physicians play active roles not only as key healthcare providers but also as sources of information and commentators on digital platforms. These shared experiences, documented and published by colleagues, significantly contributed to the development of treatment guidelines.

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was officially identified in March 2020 when the World Health Organization (WHO) declared a pandemic. Among the elderly, patients with malignant disorders were considered the population at the greatest risk of poor COVID-19 outcomes (1). Indeed, studies conducted during early pandemic experiences indicated that cancer had a substantially undesirable impact on COVID-19 outcomes, including higher mortality rates. Lung cancer and hematologic malignancies have the highest probability of serious COVID-19 complications (2,3). Because patients with hematological disorders have very different immune conditions that exhibit heightened vulnerability, more preventative measures and management programs were established during this period. As the pandemic progressively spreads to other countries, consecutive papers have declared that not all hematological malignancies bear the same risk, with varying numbers of patients (4-7).

This study aimed to investigate the impact of COVID-19 on patients with hematological disorders by documenting our single-center experience with a homogenous management approach and providing insights into patient outcomes and management strategies.

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Methods

Clinical and laboratory data, including treatment details and patient outcomes, were obtained from accessing institutional electronic medical records. The data of 285 adult patients diagnosed with COVID-19 between March 2020 and May 2023 from İstanbul University, İstanbul Faculty of Medicine were retrospectively analyzed.

No funding was used in this study, which received approval from the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (approval number: 08, date: 02.04.2021).

Only symptomatic patients were screened. All patients were screened by lung computed tomography (CT) scans and microbiologically by real-time polymerase chain reaction (RT-PCR) testing of nasal and oropharyngeal swab specimens. COVID-19 diagnosis was based mainly on lung imaging. Patients with negative RT-PCR results but diagnosed with COVID-19 based on typical clinical, laboratory, and thoracic CT imaging were also included in the study. According to the WHO's recommendations, COVID-19 illness severity was categorized as mild, moderate, and severe.

Patients: Patients were stratified according to their malignant or benign disorders, progressing to macrophage activating syndrome, experiencing thromboembolic events, necessitating intensive care unit admission, or succumbing to COVID-19.

Treatment strategies: The treatment protocol was based on the National Health Authority protocol, which included the early periods of hydroxychloroquine, azithromycin, and intravenous immunoglobulin (IVIG). Hydroxychloroquine was administered to patients with mild to moderate symptoms who also had comorbidities, while azithromycin was used in the same group if there was suspicion of bacterial superinfection. IVIG was administered to immunosuppressed patients, those with severe inflammatory responses/cytokine storms, or critically ill patients who were unresponsive to other treatments. For some patients, immune plasma was used, which is not routine.

The use of hydroxychloroquine and azithromycin was discontinued following their removal from the treatment guidelines. In a short time, the antiviral agent favipiravir was replaced by molnupiravir. For patients with cytokine storm, steroids were used as the frontline treatment. For steroid-refractory cases, anti-cytokines, such as tocilizumab or anakinra, were used, which were chosen by availability.

All patients received aspirin for a short period with a dipyridamole combination, which was changed to enoxaparin in hospitalized patients. The enoxaparin dose was increased to the therapeutic dose in patients with D-dimer levels >1000 U/mL or documented thromboembolic events.

Statistical Analysis

Continuous variables are presented as medians, and the number of categorical variables is given. The differences between groups were analyzed with X^2 test. Risk factors were evaluated using univariate and multivariate logistic regression models. The primary endpoint was the survival rate of the cohort. We evaluated the outcomes according to hematologic malignancies, age, disease status at the time of COVID-19 diagnosis, administration of monoclonal antibody, COVID-19 severity, comorbidities, and vaccination status. We also evaluated the effects of COVID-19 treatment type, thrombosis occurrence, and oxygenation status on the survival rate. Statistical analysis was performed using StataMP 17.

Results

The data collection encompassed the 3 years of the pandemic with changing management algorithms and intervening vaccination. The latter was not obligatory, and the type of vaccine was chosen according to the patient's preference.

A total of 285 patients' data were evaluated. The median age was 57 years (range: 18-87) with a male predominance (55%). The rate of COVID-19 PCR-positivity was 96%.

The majority of patients (89%) had malignant hematological disease (Figure 1). The most common hematologic disease was multiple myeloma with a ratio of 24% among malignant disorders and immune thrombocytopenic purpura with a ratio of 40% among benign disorders (Table 1). Two patients had prior solid organ transplantation, 62 had blood or bone marrow transplantation, and 43.5% had allogeneic transplantation. In 5.6% of patients, COVID-19 led to a new diagnosis of a hematologic disease.

The comorbid disorders are presented in Figure 2. The most common comorbid association was hypertension, with a frequency of 32%; diabetes mellitus and cardiovascular disorders were the followers, with a frequency of 23% and 19%, respectively.

The severity of COVID-19 was available in 133 patients. Most patients experienced mild COVID-19 severity (59.5%). Severe COVID-19 was infrequent (10.4%) and fatal at 61% ($p<0.001$). The intensive care unit (ICU) was necessary for 38 patients (13.3%), 25 of whom (8.8%) were intubated, and 28 (73.7%) died of COVID-19 ($p<0.001$).

The overall mortality rate was 17.89%. Patients aged 65 years or older were at increased risk of death ($p<0.001$). Among the disorders, patients with lymphoid malignancies had a significantly higher mortality rate compared with those with myeloid malignancies ($p=0.009$).

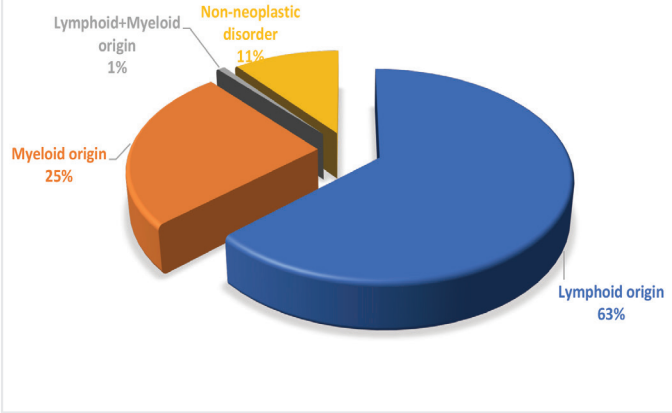

Figure 1. Distribution of hematologic disease among patients with COVID-19

COVID-19: Coronavirus disease-2019

Chronic lymphocytic leukemis (CLL) patient's had the poorest outcomes. Indeed, 11 of the 23 CLL patients died (p<0.001). The variables determined in the multivariate analysis are presented in Table 2 with the hazard ratios, p-values, and confidence intervals.

Table 1. The proportions of hematological disorders

Neoplastic hematologic diagnosis	n	Benign hematologic diagnosis	n
	254		31
Multiple myeloma	56	Immune thrombocytopenic purpura	12
Diffuse large B-cell lymphoma	24	Thrombotic thrombocytopenic purpura	5
Hodgkin lymphoma	24	Aplastic anemia	4
Chronic lymphocytic leukemia	23	Thalassemia major	4
Acute myeloid leukemia	21	PNH	3
Chronic myeloid leukemia	15	Autoimmune hemolytic anemia	2
Myelodysplastic syndrome	11	PNH + aplastic anemia	1
Follicular lymphoma	8	Immune neutropenia	1
B-cell ALL	6	Aceruloplasminemia	1
Primary myelofibrosis	6	Protein S deficiency + factor V Leiden deficiency	1
Essential thrombocythemia	6		
Low-grade NHL	5		
Mantle cell lymphoma	5		
T-cell NHL	5		
Polycythemia vera	4		
Primary central nervous system lymphoma	4		
Waldenstrom macroglobulinemia	3		
Secondary myelofibrosis	3		
T-cell ALL	3		
Hairy cell leukemia	3		
Chronic myelomonocytic leukemia	2		
Plasma cell leukemia	2		
Monoclonal gammopathy unknown significance	2		
Cutaneous B-cell lymphoma	2		
Granulocytic sarcoma	1		
Mycosis fungoides	1		
Systemic mastocytosis + marginal zone lymphoma	1		
Al amyloidosis	1		
Burkitt lymphoma	1		
Chronic myeloproliferative neoplasia	1		
Erdheim Chester disease	1		
Langerhans cell histiocytosis	1		

PNH: Paroxysmal nocturnal hemoglobinuria, ALL: Acute lymphoblastic leukemia, NHL: Non-Hodgkin lymphoma

Among thromboembolic events and coagulopathy, 10 of the 20 patients developed arterial thrombosis, 9 of the 21 patients developed venous thrombosis, 8 of the 17 patients had thrombotic microangiopathic anemia, and 9 of the 18 patients experienced disseminated intravascular coagulation died (p<0.001 for each).

Among the cytokine storm-developed patients, 20 of 81 patients died during steroid (p<0.001) and 12 of the 25 patients died during anakinra use (p=0.059).

Discussion

Since 2019, when SARS-CoV-2 originated in Wuhan, China, waves of death have occurred in nearly all countries. The initial defense strategy was to recognize the disease, implement strict protective measures, and provide appropriate treatment. Subsequently, vaccine discovery and vaccination policies were the next steps. In every stage of progress, a group of people were found to be more prone to the disease and to experience more severe forms than those initially identified. Patients with hematologic malignancies were one such group. Hematologists from various countries, through either single-center or multicenter studies,

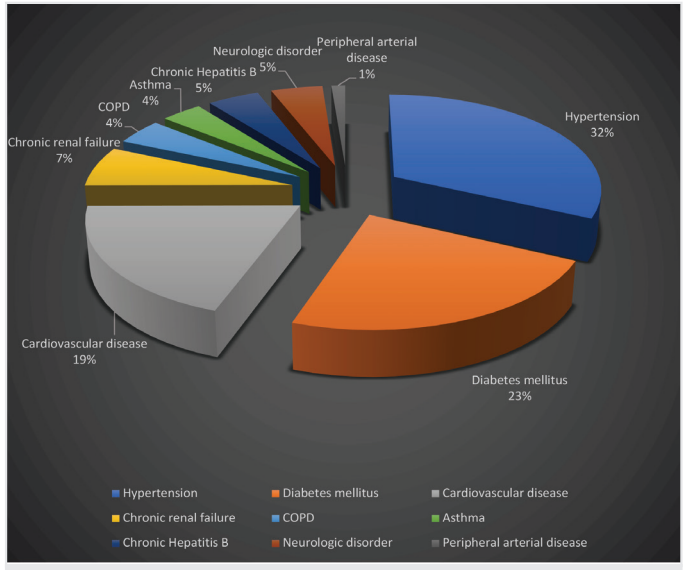

Figure 2. The associated comorbid conditions
COPD: Chronic obstructive pulmonary disease

Table 2. Hazard ratios with age, lymphoid malignancy, CLL diagnosis, disease status, severity of COVID-19, and vaccination status

Variable	HR	p	95% CI
Age ≥65	2.579937	<0.001	1.972285-6.498022
Lymphoid malignancy	2.0122485	0.051	0.9970529-4.062067
CLL diagnosis	3.533434	0.001	1.730691-7.213973
Active disease	1.782202	0.087	0.9189597-3.456348
COVID-19 severity	5.159932	<0.001	2.564944-10.38031
Unvaccinated	6.154189	<0.001	2.975884-12.72699

CLL: Chronic lymphocytic leukemia, COVID-19: Coronavirus disease-2019, HR: Hazard ratio, CI: Confidence interval

have published their experiences to define common management protocols and guidelines (8-16).

Our study primarily aimed to delineate the fatality rate among patients with various hematologic disorders by utilizing a highly homogenous team of healthcare workers and physicians. Our analysis revealed an overall mortality rate of 17.89%, which was lower than that of previously reported early experiences. However, a cohort study in Wuhan, China, covering the first month of 2020, reported a case fatality rate of 62% (17). This investigation included hospitalized patients diagnosed with hematologic malignancies who subsequently contracted COVID-19. The high fatality rate may be attributable to early experiences and the inclusion of already hospitalized patients.

Another study from the United Kingdom focused on hospitalized patients with hematologic malignancies who developed SARS-CoV-2 infection. The results revealed an overall preliminary case fatality rate of 51.5%, with most patients aged 70 years. An elevated fatality rate was observed during the early period of the pandemic, and the predominance of elderly patients, a significant risk factor for COVID-19, likely contributed to this outcome (18). The increased vulnerability of older adults to infection may stem from reduced immune function and vaccine effectiveness. Additionally, various other factors contribute to the increased risk of infections in this population, such as malnutrition, comorbidities, and weakened mucosal defenses, etc. (19).

It is well-established that various states of immune deficiency increase the risk of respiratory tract infection and poor outcomes. Patients with hematologic malignancies are particularly immunocompromised because of bone marrow infiltration and/or the type of treatment they receive, leading to conditions such as lymphopenia, neutropenia, or immune dysfunction. In the context of hematopoietic stem cell transplantation, treatments-particularly the use of corticosteroids or immunosuppressive medications-further exacerbate immune deficits. These factors contribute to the high-risk status of patients with CLL, who, as shown in our study, have significantly worse outcomes.

In our study, the primary endpoint was not hospitalization requirement, as this parameter may vary depending on the physician's initiatives and the social characteristics of the patients. However, ICU admission was a more descriptive and restrictive endpoint. We found that 13.3% of patients required ICU care, and 8.8% of these patients were intubated. A Turkish retrospective case-control study conducted during the early pandemic period reported an ICU admission rate of 22% among 156 immunocompromised patients, which was higher than in our cohort. We believe that this difference is primarily attributable to the timing of the two studies. Our study spanned the three years following the pandemic declaration, during which vaccines against SARS-CoV-2 were developed and widely administered, fundamentally changing game players (20). The difference in ICU admission rates between our study and earlier reports can be attributed to the widespread availability and administration of vaccines during our study period, which played a crucial role in reducing severe cases and mortality.

General studies involving patients with hematologic malignancies who developed COVID-19 have consistently found that mortality rates are often higher than those in otherwise healthy populations (21). In our study, the mortality rate of patients with hematologic malignancies who developed COVID-19 was 17.8%. Elderly individuals and those with lymphoid malignancies were identified as being at higher risk.

Patients with CLL exhibit intrinsic impairment of both humoral and cell-mediated immunity, which is associated with primary pathology. These conditions include hypogammaglobulinemia, disruption of T-cell subsets, and deficiencies in complement activity and neutrophil and monocyte function. Immune function is further compromised by therapy-induced immunosuppression (22). A multicenter study involving multiple countries reported high mortality rates in both watch-and-wait and treated CLL patients, with a case fatality rate of 33% among those admitted with COVID-19 (15). We also documented that outcomes for CLL patients were the worst, as 47.8% of the CLL patients succumbed to COVID-19.

A large-scale study involving 3,801 patients with hematologic malignancies reported a mortality rate of 31%. In contrast, this study found the highest mortality rate among patients with AML or myelodysplastic syndrome, reaching 40% (23). A research study assessing postvaccination risk factors has demonstrated that pre-existing medical conditions constitute a risk factor for a diminished cellular immune response following the administration of the third dose of the SARS-CoV-2 vaccine, and chemotherapy builds up a risky basis for impaired humoral immune response (24). However, in our cohort, the mortality rate was higher in patients with lymphoid malignancies.

Study Limitations

The limitations of our study include the relatively small sample size due to the single-center design, heterogeneity of the diseases, and partial data loss resulting from the retrospective design. Although we initially applied a consistent treatment approach at our center, the evolving nature of the pandemic has led to changes in treatment protocols worldwide. As a result, our patient care practices were also adapted based on the latest available literature.

Conclusion

In conclusion, although mortality was significantly higher in the unvaccinated group in our cohort, there is a clear need for documentation of vaccination efficacy. Clinically, several patients contracted SARS-CoV-2 during treatment, and viral clearance required time. However, the absence of COVID-19 severity resembling the initial phase of the pandemic may be an indirect indicator of the effectiveness of vaccines.

Ethics

Ethics Committee Approval: The ethics committee approved the study by the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (approval number: 08, date: 02.04.2021).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions: Surgical and Medical Practices - S.E., M.M., İ.Y.H., M.N.Y., M.N.; Concept - İ.Y.H., M.N.Y., M.N., S.K.B.; Design - M.Ö., S.K.B.; Data Collection or Processing - S.E., S.S.E., M.M., İ.Y.H., M.N.Y., M.N.; Analysis or Interpretation - S.E., M.Ö., S.K.B.; Literature Search - S.E., S.S.E., M.M., S.K.B.; Writing - S.E., S.K.B.

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

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The Impact of Sarcopenia on the Early Mortality and Survival of Patients Undergoing Primary Repair for Perforated Peptic Ulcer

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ABSTRACT

Introduction: Sarcopenia is a significant prognostic factor that influences morbidity and mortality, particularly in patients with cancer. The current study aimed to investigate the impact of sarcopenia on early mortality and survival among patients undergoing surgery for perforated peptic ulcers at our clinic.

Methods: This retrospective study was conducted at the Mersin University Faculty of Medicine, Department of General Surgery between January 1st 2010 and December 31st 2021. The study included adult patients aged >18 years who were diagnosed with peptic ulcus perforation and underwent Graham patch repair (primary closure + omental patch). Sarcopenia was assessed based on the patients' demographic data, nutritional status, and preoperative computed tomography scans, and mortality and survival analyses were performed to compare patients with and without sarcopenia.

Results: A total of 238 patients were included in the study. Of these, 165 were male (69.3%) and 73 were female (30.7%). Mean age was 50.7±16.9. The median age of the non-survivors was 63.6 years, compared to 48.4 years in those with prolonged survival ($p<0.001$), whereas the median survival of the entire sample was 84.45%, specifically 64.41% for the patients with sarcopenia and 91.06% for those without sarcopenia ($p<0.001$).

Conclusion: This study identified advanced age and sarcopenia as factors that independently decreased survival among patients undergoing primary repair for perforated peptic ulcers.

Keywords: Peptic ulcer perforation, sarcopenia, mortality, survival

Introduction

Sarcopenia is typically considered a geriatric condition that is characterized by low muscle mass and diminished muscle function (strength or performance) (1). The reported prevalence rates around the globe range from 3% to 30% in the elderly population (2). Unlike cachexia, sarcopenia does not necessitate the presence of an underlying condition, and so many cases of sarcopenia do not have cachexia. Several authors have used the term secondary sarcopenia to describe sarcopenic conditions associated with diseases such as organ failure, inflammatory diseases, malignancies, and endocrine disorders (3-5).

Sarcopenia can be characterized as 2 standard deviation (SD) points below the mean appendicular muscle mass in healthy young adults. Sarcopenia and body composition are often assessed using dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (6).

There have been numerous studies in the literature investigating sarcopenia and cachexia, and its prevalence in oncological patients in particular, reporting it to be a significant prognostic factor affecting morbidity and mortality (7). Although it is believed that there may be a higher risk of sarcopenia in cases with gastrointestinal tract disorders resulting from inadequate nutrition following dyspepsia and malabsorption, very few studies to date have addressed this issue. To date, studies have tended to focus on patients with inflammatory bowel disease and hepatopancreaticobiliary diseases (8), reporting a prevalence of sarcopenia of 32.0% in those with gastrointestinal tract disorders (8),

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whereas studies of patients with peptic ulcers and perforated peptic ulcers are relatively more scarce (9). Most studies of sarcopenia report a close relationship with mortality (10).

The current study aimed to investigate the effect of sarcopenia on early mortality and survival among patients undergoing surgery for peptic ulcer perforation in our clinic.

Methods

This retrospective study was conducted at the Mersin University Faculty of Medicine, Department of General Surgery between January 1st 2010 and December 31st 2021. The study included adult patients aged >18 years who were diagnosed with peptic ulcus perforation and underwent Graham patch repair (primary closure + omental patch) (Figure 1). Information on 238 patients who met the study criteria was obtained from the hospital archives. On September 2nd, 2022, the study was approved by the Mersin University Faculty of Medicine Ethics Committee (approval number 2022/610, date: 31.08.2022). Consent forms were obtained from all patients. Patients under the age of 18, those without preoperative CT imaging, those who were preoperatively-postoperatively diagnosed with malignancy, and those who underwent other surgical procedures were excluded from the study. Patients with unreliable data and for whom we were not able to follow-up were also excluded.

The patient demographics, including age, sex, weight, and height, were recorded, and body mass index (BMI) was calculated. Based on the BMI, patients were categorized as underweight, normal weight, overweight, or obese. For the calculation of the average hounsfield unit (AHU), validated sarcopenia indicators and measurements of the area and density of the right and left psoas muscles at the L3 vertebral level were performed by a single radiologist at our hospital, following the appropriate guidelines in literature (Figure 2) (11-13). For the area and density calculations, the psoas muscle was examined through axial sections at the level of the L3 vertebra. After outlining the psoas muscle and calculating the Hounsfield units and psoas area, the AHU was calculated using the following formula:

Left AHU = (Left Hounsfield Unit × Left Psoas Area)/Total Psoas Area;

Right AHU = (Right Hounsfield Unit × Right Psoas Area)/Total Psoas Area;

AHU = (Left AHU + Right AHU) / 2

Patients were categorized as sarcopenic or non-sarcopenic based on the sex-specific lower quartile thresholds defined by the AHU calculation and were assigned to separate groups. The pathological threshold value for females is <20.3 HU, for males is <18.8 HU.

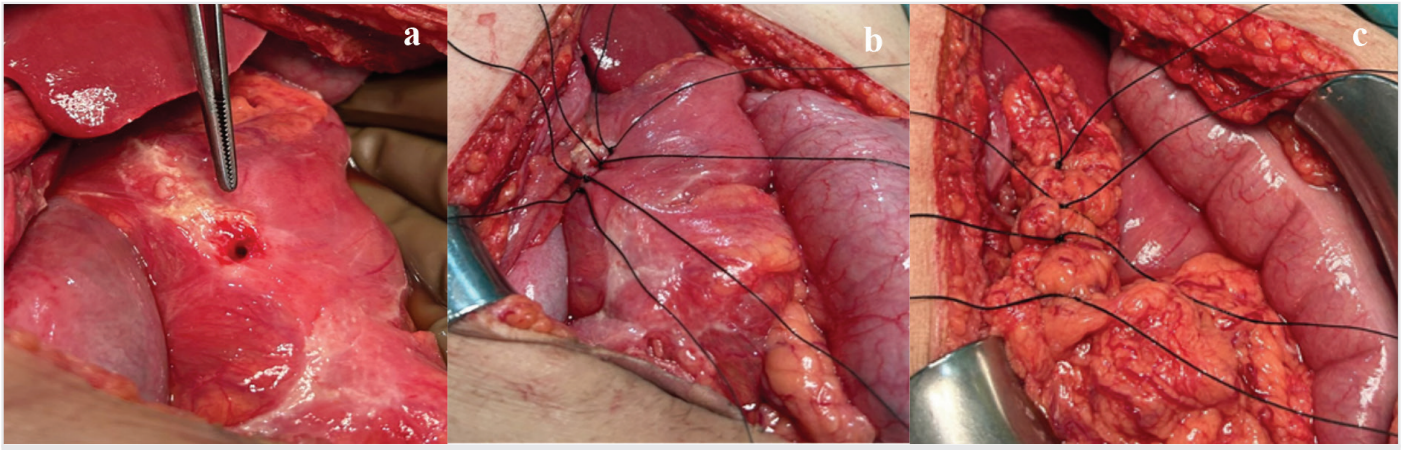

Figure 1. Graham rafi (primary repair + omental patch procedure). (a) Perforated area, (b) primary repair, (c) omental patch procedure. Informed consent was obtained from the patient to use the images for scientific purposes

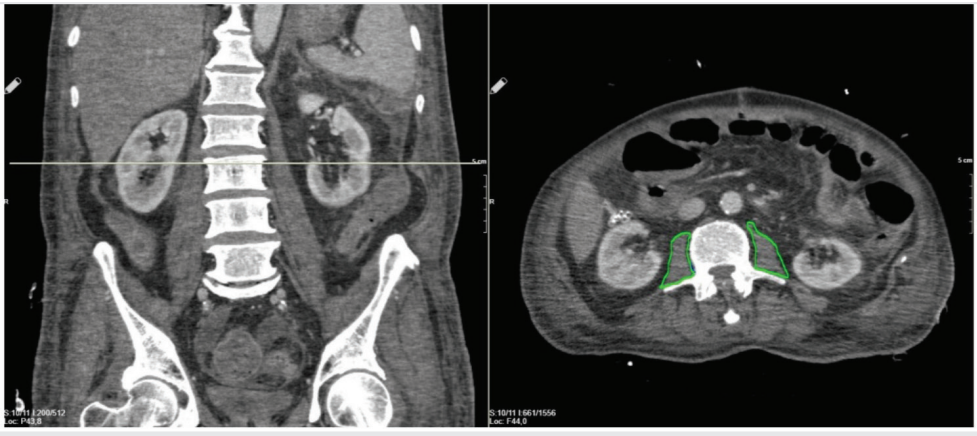

Figure 2. Hounsfield unit average calculation and psoas muscle size measurement

The non-survivors were considered a separate group, and the survival duration from the time of surgery was calculated. The patients were subsequently divided into survivors and non-survivors. The survival time of both groups was calculated in days, and mortality within the first 30 days (first month) was defined as early mortality.

Statistical Analysis

The data were analyzed using the www.e-picos.com software and the MedCalc statistical package program. For data analysis, continuous variables were presented as mean and SD and minimum and maximum values, while categorical variables were represented as frequencies and percentages. The Student's t-test was used to compare the means of the independent groups, and the chi-square test was used to evaluate the relationship between categorical variables. The odds ratio for the sarcopenia variable, which is hypothesized to be associated with early mortality/survival, was calculated at a 95% confidence interval (CI). Total survival curves were generated using the Kaplan-Meier method, and differences based on risk factors were identified using the log-rank test, with hazard ratios and corresponding 95% CIs reported. Statistical significance was determined using a p-value 0.05.

Results

Two hundred thirty-eight patients were included in the study. Of these, 165 were male (69.3%) and 73 were female (30.7%). Mean age was 50.7±16.9. Considering patient's BMI; 75 of the patients were underweight (31.5%), 131 were normal weight (55%), 27 were overweight (11.35%), and 5 were obese (2.1%). According to AHU measures, 59 of the patients were sarcopenic and 179 were not sarcopenic. The median age of mortality was 65.5. The median age of survival was 49.2. Patient age and early mortality rates were highly correlated, and a significant statistical difference was found.

No significant relationship was identified between early mortality and sex or BMI ($p>0.05$). A significant relationship was identified between the presence of sarcopenia and early mortality ($p<0.05$), with sarcopenia identified in 54.5% of the patients who died and 21.8% of the survivors (Table 1).

A survival analysis revealed that the median age of patients who died during the follow-up period was 63.6 years, compared with 48.4 years among the survivors. No significant relationship was identified between survival and gender or BMI ($p>0.05$). A significant relationship was noted between the presence of sarcopenia and survival ($p<0.05$), with a sarcopenia rate of 56.8% recorded among those who died in the long term compared with 18.9% among the survivors (Table 2).

The number of patients with sarcopenic who experienced early mortality was 4.32 times greater than that of patients who did not experience early mortality ($p<0.05$) (Table 3).

In the survival analysis, the number of sarcopenic patients who died was 5.63 times higher than the number of patients who did not die ($p<0.05$).

In the comparison of the survival curves in Table 4, the median survival is presented with a 95% CI, and the overall survival among those who underwent surgery for a perforated peptic ulcer was 84.45%. In the log-rank test comparing the two survival curves, mortality was noted in 21 of the 59 patients with and 16 of the 179 patients without sarcopenia. The chi-square statistic for this case was 25.33, with a p-value 0.05 (<0.001).

The study was concluded on day 4,134, and as can be seen in Figure 3, the probability (%) of survival decreased over time. The number of at-

Table 1. Relationship of demographics and characteristics with early mortality

	Total, (n=238)	EM (-), (n=216)	EM (4), (n=22)	p
Age	50.7	49.2	65.5	**<0.001**
	n (%)	**n (%)**	**n (%)**	
Sex				
Male	165 (69.3)	151 (69.9)	14 (63.6)	0.54
Female	73 (30.7)	65 (30.1)	8 (36.4)	
BMI				
Underweight	75 (31.5)	65 (30.1)	10 (45.5)	0.29
Normal	131 (55)	121 (56)	10 (45.5)	
Overweight	27 (11.3)	26 (12)	1 (4.5)	
Obesity	5 (2.1)	4 (1.9)	1 (4.5)	
Sarcopenia				
(-)	179 (75.2)	169 (78.2)	10 (45.5)	**0.001**
(+)	59 (24.8)	47 (21.8)	12 (54.5)	

BMI: Body mass index, EM: Early mortality

Table 2. Evaluation of socio-demographic and clinical characteristics in relationship with survival

(n=238)	Survival, (n=201)	Ex, (n=37)	p
Age	48.4	63.6	**<0.001**
	n (%)	**n (%)**	
Sex			
Male	144 (71.6)	21 (56.8)	0.07
Female	57 (28.4)	16 (43.2)	
BMI			
Undeweight	59 (29.4)	16 (43.2)	0.37
Normal	115 (57.2)	16 (43.2)	
Overweight	23 (11.4)	4 (10.8)	
Obesity	4 (2)	1 (2.7)	
Sarcopenia			
(-)	163 (81.1)	16 (43.2)	**<0.001**
(+)	38 (18.9)	21 (56.8)	

BMI: Body mass index

Table 3. Evaluation of early mortality/survival status in relation to sarcopenia

Variable	OR	Lower (95% CI)	Upper (95% CI)	p
Early mortality				
Sarcopenia	4.32	1.76	10.61	**p<0.05**
Survival				
Sarcopenia	5.63	2.69	11.81	**p<0.05**

OR: Odds ratio, CI: Confidence interval

risk patients indicates the number of patients who are at risk of an event at each time point (day).

Among the patients with sarcopenia, 59 were considered at risk at the outset of the study (day 0), and by day 1,000, the number of patients considered at risk was 38. Throughout the period from day 0 to day 1,000, mortality or censored data (no mortality) were observed in 21 patients. Among the non-sarcopenic patients, 179 were considered at risk at the outset of the study (day 0). By day 1,000, 147 patients were considered at risk was 147. Throughout the period from day 0 to day 1,000, mortality or censored data were observed in 32 patients.

Discussion

In the present study, advanced age and sarcopenia were identified as significant factors influencing early mortality and survival among patients with perforated peptic ulcers, and the inclusion of such a wide age range in the study adds significance to its findings. In a study investigating mortality and sarcopenia in patients aged 65 years and over (6), sarcopenia, like other prognostic factors, was found to be valuable in predicting mortality in elderly patients with perforated peptic ulcers. However, in patients older than 65 years, the direct influence of sarcopenia may be masked by advanced age and the presence of multiple comorbidities. In the present study, the median age of the patients who died was 63.6 years, and 48.4 years among the survivors.

Perforated peptic ulcers have been reported in the range of 3.8-14 per 100,000 (14), with a mortality rate of 8-27% that increases with age (15-18). Several studies have investigated the prognostic factors that influence mortality (16-18), and those identifying the factors that contribute to perforation and mortality, especially in patients with peptic ulcers, can be considered of critical importance. In the present study, sarcopenic patients were found to have a 7.32-fold greater risk of mortality than non-sarcopenic patients. Therefore, sarcopenia directly influences mortality. The median age was 63.6 years among the non-survivors, 48.4 years among those with prolonged survival, 65.5 years among patients who experienced early mortality, and 49.2 years among the survivors. It is necessary to consider how sarcopenia can be prevented in patients with peptic ulcers, especially the elderly, and how mortality can be reduced in the event of ulcer perforations.

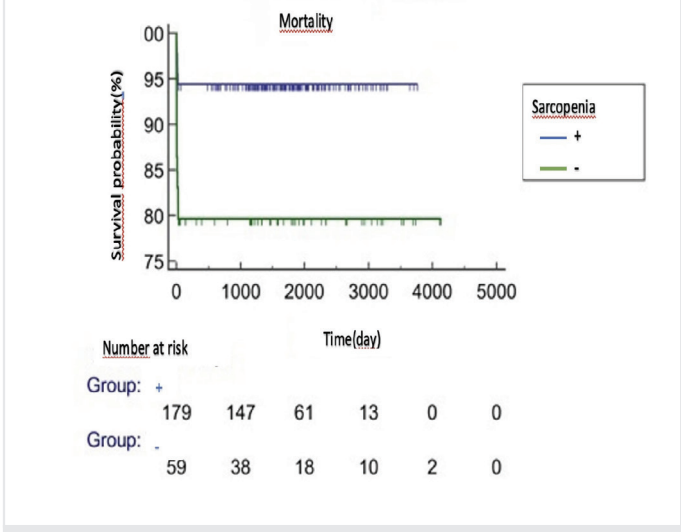

Figure 3. Sarcopenia mortality relationship

Peptic ulcers and perforations are characterized by inflammation and damage starting from the mucosa and extending to greater depths. It is believed that mechanisms involving proteins and amino acids that begin in the mucosa and contribute to the healing process may be inadequate in patients with sarcopenia (19). The defects in the protective and reparative mechanisms caused by sarcopenia can lead to acute abdominal conditions such as hollow organ perforation and mesenteric ischemia (20). In the early stages of peptic ulcer, the provision of protein-rich supplements for sarcopenia, alongside proton pump inhibitors and the standard medications used for *Helicobacter pylori* eradication, appears reasonable (21). There is little evidence supporting an increase in muscle mass in older adults taking nutritional supplements, although sarcopenia can be found in all inadequately nourished patients (22), highlighting the need for further prospective studies involving patient populations with peptic ulcers in particular.

The pathophysiology of sarcopenia involves factors such as neuromuscular aging, sarcopenia as a component of cachexia, inflammation, advanced age, immobility and confinement to bed, and sarcopenic obesity (22). For instance, in SO, not only low muscle mass but also the combination of low muscle and high fat mass has been identified as influential. In a study by Choi et al. (23), sarcopenic obesity was found to be associated with a greater prevalence of peptic ulcer disease, with an increased risk of developing idiopathic peptic ulcer disease in patients with low muscle and high fat mass. This indicates that not only sarcopenia but also various conditions related to malnutrition is contributing factors to the disease.

Study Limitations

This study has some limitations, including its retrospective nature, limited opportunity for postoperative follow-up, and the disregard for morbidities due to the lack of data.

Table 4. Comparison of survival curves (log-rank test) and HRs with 95% CI

	Long term mortalityn (%)	Survival, n (%)	Mean survival days (95% CI)	HR, (95% CI)	Log-rank (p)
Sarcopenia					
(-) (<32.65)	16 (8.94)	163 (91.06)	3424.8 (3265.1-3584.5)	7.32 (3.37-18.89)	<0.001
(+) (≥32.65)	21 (35.59)	38 (64.41)	2707.1 (2216.3-3197.9)		
Total	37 (15.55)	201 (84.45)	3496.8 (3307.1-3686.2)		

CI: Confidence interval, HR: Hazard ratios

Conclusion

In conclusion, advanced age and sarcopenia are factors that can independently decrease survival in patients undergoing primary repair for perforated peptic ulcers. Determining the risk of sarcopenia among patients with peptic ulcers is particularly important for screening and preventive measures.

Ethics

Ethics Committee Approval: This study was approved by the Mersin University Faculty of Medicine Ethics Committee (approval number 2022/610, date: 31.08.2022).

Informed Consent: Consent forms were obtained from all patients.

Footnotes

Authorship Contributions: Surgical and Medical Practices - Ö.Ö., E.R., H.B.; Concept - Ö.Ö., E.R., H.B., D.T.; Design - Ö.Ö., E.R., H.B., D.T.; Data Collection or Processing - H.B., S.E., E.E.; Analysis or Interpretation - Ö.Ö., E.R., H.B., E.E.; Literature Search - Ö.Ö.; Writing - E.R., H.B., D.T.

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

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Characteristics of Pediatric Patients Following the Kahramanmaraş Earthquake: Experience of a Major Referral Pediatric Intensive Care Unit Outside the Disaster Zone

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ABSTRACT

Introduction: Earthquakes are unpredictable catastrophes that lead to an increase in critical care requirements, particularly for children. Concurrently, these often calamities decimate indispensable healthcare infrastructure, as exemplified by the Kahramanmaraş earthquake. This study aimed to examine the clinical features and outcomes of pediatric patients admitted to a remote pediatric intensive care unit (PICU) after a post-earthquake. This study further attempts to highlight the challenges in post-disaster healthcare provision.

Methods: The research involved a retrospective examination of pediatric patients transferred to the PICU of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital following the Kahramanmaraş earthquake on February 6, 2023.

Results: This study analyzed 35 pediatric patients admitted to the PICU, with an average age of 12 years. The median Glasgow Coma Score upon admission was 14, and the median Pediatric Trauma Score was 6. Injuries included head, spine, pelvis, and limb fractures, as well as lung injuries, renal bleeding, and splenic bleeding. The median creatine kinase level was 6591 U/L, and the median hemoglobin and serum creatinine levels were 11.8 g/dL and 0.45 mg/dL, respectively. All patients were successfully discharged from the PICU (median stay: 13 days. Twelve patients received hyperbaric oxygen therapy (HOT), with a median of 23 sessions. Only one patient required amputation, highlighting the potential of HOT for preventing limb loss.

Conclusion: Earthquakes pose significant challenges and necessitate rapid and effective critical care responses, particularly for children. The current study highlights the importance of a multidisciplinary approach in managing pediatric critical care needs during and after a disaster. This underscores the efficacy of HOT in preventing limb loss and the significance of antimicrobial treatment and postdisaster infection control measures. Furthermore, this study addresses the complexities of patient transfers and the identification of accompanying family members during disasters.

Keywords: Earthquake aftermath, emergency pediatric management, pediatric intensive care unit, post-earthquake healthcare, trauma

Introduction

Türkiye is considered one of the most seismically active regions in the world (1). The most recent earthquakes occurred on February 6, 2023, with their epicenter in Kahramanmaraş, measuring 7.7 and 7.6 in magnitude, respectively, resulting in significant destruction and losses nationwide (2). This natural disaster severely affected infrastructure and healthcare services, with notable consequences for hospitals and healthcare workers in the region (3).

Natural disasters are unpredictable events that cause widespread damage (4). In such cases, urgent and critical care services are needed for many individuals, necessitating the prioritization and management of healthcare services. Children are also significantly affected by natural disasters and require immediate and effective critical care services (5-9).

This study aimed to examine the unusual conditions following the Kahramanmaraş earthquake, treatment processes, and transfer of pediatric patients. Additionally, we intend to elucidate the processes

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experienced in pediatric intensive care services in response to this unexpected situation in detail.

Methods

This retrospective study was conducted at the third pediatric intensive care unit (PICU) of University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital. The 16-bed unit is located at a significant geographical distance from the earthquake zone and is one of the centers where numerous patients were transferred nationwide after the earthquake. The unit accepts approximately 500 patients each year and serves as a comprehensive referral center.

The demographic and clinical characteristics of the patients were obtained from the patient and electronic medical records. The vaccination status of the patients was assessed based on existing vaccination records.

Inclusion Criteria

- Transferred for advanced treatment from the earthquake-affected region.

- Requiring treatment in the PICU.

Exclusion Criteria

- Having intensive care needs unrelated to the trauma caused by the earthquake, despite coming from an earthquake-affected area (e.g., pneumonia, bronchiolitis).

- Transferring children to other units within the hospital.

Ethical Declaration

This study was conducted with the approval of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee (approval number: 226, date: 24.05.2023). All procedures performed in this study conformed to the ethical standards of the institutional and national research committee and with the 1975 Helsinki Declaration and its subsequent amendments.

Statistical Analysis

Statistical analyses for this study were conducted using SPSS version 20 (IBM Corp., Armonk, NY). The normal distribution of data was assessed using the Kolmogorov-Smirnov test. Participants' characteristics, including age, Glasgow Coma Scale (GCS) scores, vital signs, laboratory values, duration of mechanical ventilator use, continuous veno-venous hemodiafiltration (CVVHDF) duration, and hyperbaric oxygen therapy (HOT) sessions, are presented as median (range). In contrast, the laboratory values are presented as median (interquartile range). The relationships between serum creatine kinase, hemoglobin, and albumin levels and the number of days in the intensive care unit (ICU) after admission were determined using the Pearson correlation test. Results were considered statistically significant when the p-value was less than 0.05.

Results

The mean age of the 35 children admitted to the ICU was 12, with a distribution of 15 men and 20 women. The average time to admission to the ICU after the earthquake was four days. The median GCS score of these patients was 14, and the median Pediatric Trauma Score (PTS) was 6. In the classification according to trauma sites, three patients had head injuries, one of whom had a skull base fracture. Two patients had spinal fractures, and two others had sacrum and pelvis fractures. Nine patients had upper extremity trauma, including two with fractures and seven with crush injuries. Among the 24 patients with lower extremity trauma, four had fractures, and five (one bilateral) had undergone amputations. Initially, fasciotomy was performed on seven of these patients. Two patients had spinal fractures at the L1 and L1-T12 levels, two had sacral fractures, and two had pelvic fractures. Two patients had pneumothorax, three had lung contusions, and one had alveolar hemorrhage. Additionally, one patient experienced bilateral kidney and splenic bleeding (Table 1).

Based on laboratory values upon admission to the ICU, the median creatine kinase level was 6591 U/L. The highest value measured was >202,000. The median hemoglobin level was 11.8 g/dL, and the serum creatinine level was 0.45 mg/dL (Table 2).

All patients were discharged from the PICU and subsequently from the hospital. The median length of stay in the ICU was 13 days. Five patients were intubated and all were successfully extubated. Additionally, three patients required CVVHDF (creatinine values of the patients; 3.36, 3.37, and 0.59 mg/dL. In the case of the third patient, CVVHDF was initiated at the hospital in an earthquake-affected area where the initial intervention occurred. A total of 27 patients (77.1%) patients underwent surgical interventions during the intensive care course. The most commonly performed procedure was debridement (23 patients; 65.7%). Twelve patients received HOT. The median number of treatment sessions administered was 23, with the number of sessions ranging from 20 to 53. Only one patient required amputation as a result of treatment, involving the distal joint of the fourth finger (Table 3).

When examining the relationship between the admission day to the ICU and laboratory tests, a negative correlation was observed for hemoglobin levels (rho: -0.54, $p<0.05$), serum albumin (rho: -0.5, $p<0.05$), and creatine kinase (rho: -0.59, $p<0.05$).

Microbiological culture samples taken upon arrival at the patients revealed microbial growth in 10 patients, nine of whom presented 4

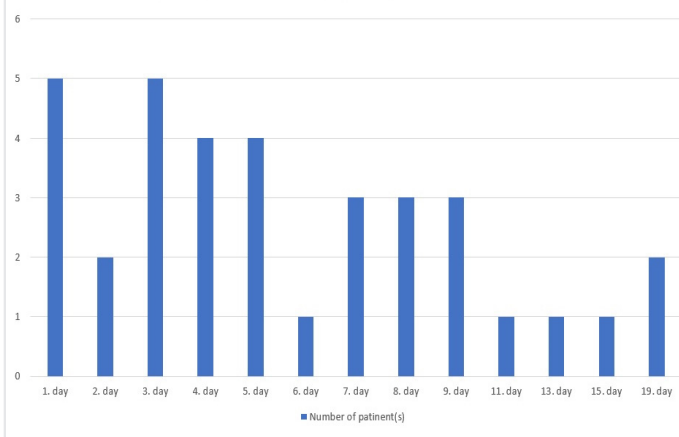

Figure 1. Number and admission days of patients following the earthquake

days after the earthquake. Microorganism growth was identified in blood, urine, and wound-site and tissue cultures. In wound cultures, antibiotic-resistant strains of *Acinetobacter baumannii* and *Klebsiella pneumoniae* were detected (other growing organisms included: blood; *Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus haemolyticus, Staphylococcus aureus, Bacillus cereus, Bacillus circulans,* tissue culture; *Escherichia coli, Citrobacter koseri, Pseudomonas aeruginosa*, urine; *Candida albicans*).

Post-Earthquake Process in the Pediatric Intensive Care Unit

Following a devastating natural disaster like an earthquake, the healthcare system was forced to accommodate an increasing number of injured patients, particularly vulnerable groups such as children. The hospital's 16-bed PICU had to rapidly expand its capacity to treat more critically ill children.

Initially, the hospital administration decided to increase the PICU capacity from 16 to 32 beds and later to 48 beds. Based on this decision, a unit that initially operated as intermediate-level pediatric intensive care was transformed into a third-level PICU. Intensive care nurses from the cardiovascular surgery ICU were also included in the process.

Table 1. Demographic and clinical characteristics of patients admitted to ıntensive care unit following earthquake

Earthquake victims	35
Age*	12 (0-17)
Gender	
Male	15 (42.8%)
Female	20 (57.2%)
GCS*	14 (6-15)
PELOD-2 score*	0 (0-10)
PTS*	6 [(-8)-8)]
Vital signs	
Heart rate (beats per minute)	109 (154-68)
Systolic arterial pressure (mmHg)	117 (142-82)
Diastolic arterial pressure (mmHg)	70 (96-46)
Oxygen saturation level (%)	98 (100-93)
Respiratory rate (breaths per minute)	21 (28-12)
Trauma site	
Head	3 (8.5%)
Thorax	4 (10.4%)
Abdomen	2 (5.7%)
Upper extremity	9 (25.7%)
Lower extremity	24 (68.5%)
Spinal	2 (5.7%)
Sacrum	2 (5.7%)
Pelvis	2 (5.7%)
Amputation	
Upper extremity	1 (2.8%)
Lower extremity	4 (11.4%)

*Median values (range),
CVVHDF: Continuous veno-venous hemodiafiltration, HOT: Hyperbaric oxygen therapy, IMV: Invasive mechanical ventilation, PICU: Pediatric intensive care unit

Table 2. Initial laboratory results of patients admitted to ıntensive care unit following earthquake

Whole blood count	
White blood cell (cells/µL)	12.2 (6)
Hemoglobin (g/dL)	11.8 (2.4)
Platelet count (platelets/µL)	296 (153)
Coagulation parameters	
Interquartile range	1.1 (0.1)
APTT	29.6 (7.65)
Fibrinogen (mg/dL)	527 (191)
D-dimer (ng/mL)	3.73 (3.8)
Serum biochemistry	
Blood urea nitrogen (mg/dL)	21.9 (40.3)
Serum creatinine (mg/dL)	0.45 (0.28)
Serum uric acid (mg/dL)	2.65 (2.95)
Alanine aminotransferase (U/L)	119 (152)
Aspartate aminotransferase (U/L)	208 (462)
Albumin (g/dL)	32 (8.7)
Creatine kinase (U/L)	6591 (24058)
Amylase (U/L)	55 (56)
Lipase (U/L)	32 (75)
Sodium (meq/L)	137 (6)
Potassium (meq/L)	4.2 (0.9)
Calcium (meq/L)	8.5 (1.3)
Phosphorus (meq/L)	3.6 (1.2)
C-reactive protein (mg/L)	55 (134)
Procalcitonin (ng/mL)	0.4 (2.8)
Blood gas analysis	
pH	7.45 (0.1)
PCO_2 (mmHg)	39 (7.7)
Bicarbonate (mmol/L)	27 (4.2)
Base excess (mmol/L)	2.6 (3.8)
Lactate (mmol/L)	1.4 (0.8)

*The data in the table is presented as median (interquartile range), APTT: Activated partial thromboplastin time

Table 3. Interventions and treatment processes in PICU

Surgical intervention [number of patient (%)]	27 (77.1%)
Fasciotomy opening/closure	7 (20%)
Fracture repair	6 (17.1%)
Amputation	5 (14.2%)
Flap surgery	4 (11.4%)
Debridement	23 (65.7%)
Patients who received HOT [number of patient (%)]	12 (34.2%)
Number of HOT therapy*	23 (20-53)
IMV (number of patient (%)]	5 (14.2%)
The length of IMV (day)*	6 (1-68)
CVVHDF [number of patient (%)]	3 (8.5%)
The length of CVVHDF (hour)*	286 (154-418)
The length of stay in PICU*	13 (1-103)

*Median values (range),
CVVHDF: Continuous veno-venous hemodiafiltration, HOT: Hyperbaric oxygen therapy, IMV: Invasive mechanical ventilation, PICU: Pediatric intensive care unit

The interdisciplinary team (including pediatric surgery, orthopedics, plastic surgery, cardiovascular surgery, pediatric infectious diseases, pediatric nephrology, pediatric psychiatry, hyperbaric and underwater medicine, and social healthcare workers) coordinated their efforts during morning rounds held at 09.00 a.m. daily. The hospital administration coordinated with local and regional authorities and other hospitals for the transfer of non-critical patients and for the reconstruction of earthquake victims.

Discussion

Earthquakes are natural disasters that simultaneously affect many individuals. Such events necessitate the simultaneous treatment of many critically ill children. The current study examined the clinical findings, treatment processes, and outcomes of child earthquake survivors admitted to the ICU after the earthquake.

First, all child earthquake survivors admitted to the ICU were successfully discharged from the PICU. Survival among all patients is the most critical finding of this study. After a catastrophic event like an earthquake, these children were able to continue their lives by being transferred to a hospital away from the earthquake-affected area. This emphasizes the importance of critical patient care.

Another critical finding was the efficacy of HOT. HOT is a preferred adjunctive treatment for critically compromised tissue oxygenation. Crush injuries, compartment syndrome, and other acute traumatic ischemic events are among the primary conditions in which this treatment is applied (10). Prior to the earthquake, children who were perfectly healthy were at risk of limb loss due to crush injuries they suffered during the earthquake. Among the 35 patients referred to our unit, five (14%) experienced limb loss as a result of amputation. However, only one of the 12 patients who received HOT underwent amputation, resulting in the loss of the distal joint of the fourth finger. After an earthquake, not only physical health but also quality of life is of great importance. One of the reasons for the high number of patients transferred to our hospital was the availability of HOT. The results of our research emphasize the critical importance of HOT, which has the potential to prevent limb loss in crush injuries following earthquakes.

Ollowing an earthquake, critically ill children in the earthquake-affected region were rescued from the rubble. Elevated acute creatine kinase levels associated with crush injuries are a significant complication in earthquake victims (11). Because the rescue operations continued for days, child admissions occurred at different time intervals and under changing clinical conditions. In the initial days, patients had higher creatine kinase levels, and as the admission day progressed, a decrease in these values was observed, indicating a negative correlation.

Immediately after the earthquake, patients were rapidly transferred to other cities. However, in the subsequent days, healthcare services in the earthquake-affected region were swiftly organized; initial treatments were administered there, and then transfers were made. We attribute this change in treatment to the effect of fluid therapy administered before transfer to earthquake-stricken regions. Thanks to this treatment, the patients' urine output and creatine kinase levels decreased before being admitted to our unit.

The presence of resistant pathogens in children after an earthquake is a significant issue (12). Microbiological culture results indicate a high-risk of post-earthquake infection, particularly in the presence of pathogens with high antibiotic resistance. Therefore, it emphasizes the importance of appropriate antimicrobial treatment practices and infection control measures. Tetanus, which has a high incidence of injury, poses a risk following an earthquake disaster (13). Reviewing tetanus immunoprophylaxis and vaccination programs is important for protecting patients against post-earthquake health risks. In this study, tetanus immunoglobulin was provided to patients with incomplete vaccine doses, and both tetanus immunoglobulin and tetanus vaccine were administered to patients with unidentified or migrant identities to ensure tetanus protection.

An earthquake affects not only children but also their parents and close relatives. Therefore, the transfer of child patients from different cities was an important process. Determining the relationship of those accompanying children is of great importance. Additionally, family members who had lost their identities during the earthquake were considered. Therefore, after the intensive care needs of the patients were resolved, the identification of relatives accompanying the children was carried out in collaboration with local authorities and social services agencies. The process for identifying relatives of children living in Türkiye as migrants was longer.

Patients with identified identities were transferred to the service along with their identified relatives. Patients without accompanying relatives and migrant patients with relatives in the process of identity verification were placed in the service under the supervision of social workers. Thus, the safe and orderly placement of children affected by the earthquake in the services was ensured. Throughout this process, a sensitive and effective approach to the needs of patients and their families was demonstrated.

We believe that this study can serve as a useful guide by providing essential information on the management of pediatric critical care needs following an earthquake and aiming to better understand the processes in the field of pediatric critical care in disaster situations. The findings emphasize the importance of a multidisciplinary approach in the management of pediatric critical care needs after a disaster.

In disaster situations, effective collaboration among healthcare providers, local authorities, and social service agencies is of great importance for providing critical pediatric care services. In this study, issues such as service transfer processes and the identification of patient relatives were successfully managed through the coordination of all relevant parties.

Study Limitations

Our study has some limitations. First, this was a single-center study, and the generalizability of the findings may be limited. Conducting more comprehensive, multicenter studies on the management of pediatric critical care needs after earthquakes will contribute to the knowledge in this area. Additionally, our study does not provide information about the long-term outcomes and quality of life of patients. Future studies evaluating the long-term outcomes of pediatric critical care patients

after earthquakes and the changes in their quality of life could make significant contributions to the literature in this field.

Conclusion

This study aimed to examine the management of pediatric critical care needs following the Kahramanmaraş earthquake, with the goal of better understanding and managing pediatric critical care processes in disaster situations. Additionally, the findings highlight the high survival rates of pediatric earthquake survivors in intensive care and underscore the potential of HOT for preventing limb loss in crush injuries.

Effective collaboration and coordination among post-disaster healthcare providers, local authorities, and social service organizations are of paramount importance. This study addresses topics such as patient transfer processes and post-intensive care support, emphasizing the critical nature of this collaboration and coordination.

The findings of this study shed light on the importance of a multidisciplinary approach in managing pediatric critical care needs following disasters. Furthermore, it serves as a valuable guide for enhancing the understanding of pediatric critical care processes during disasters.

Ethics

Ethics Committee Approval: This study was conducted with the approval of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee (approval number: 226, date: 24.05.2023).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions: Surgical and Medical Practices - M.Ç., M.A.K., S.Y.; Concept - M.Ç., R.G., M.Çet.; Design - M.Ç., R.G., M.Çet.; Data Collection or Processing - M.A.K., S.Y.; Analysis or Interpretation - M.A.K., S.Y., M.Çet.; Literature Search - S.Y., R.G.; Writing - M.Ç.

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The Importance of Body Fat Composition Evaluated by Computed Tomography and Its Prognostic Significance in Patients with Testicular Cancer

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ABSTRACT

Introduction: To investigate the relationship between visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area (SMA) ratios and testicular cancer stage.

Methods: Between 2018 and 2023, 94 patients with testicular cancer were evaluated for demographic data, pathological results, and cancer stages. VAT, SAT, and SMA were measured in cm^2 using computed tomography (CT) scans. The ratios of SMA/SAT, SMA/VAT, and SAT/VAT were calculated to assess their relationships with cancer stage.

Results: A statistically significant moderate positive correlation was found between tumor stage and the VAT/SAT ratio (r=0.35, p=0.001). The mean VAT/SAT ratio was 0.64±0.43 for stage 1 tumors, 0.81±0.41 for stage 2 tumors, and 1.32±0.29 for stage 3 tumors, indicating statistically significant differences (p=0.001). Comparisons of the groups revealed that the VAT/SAT ratio was significantly higher in stage 3 tumors than in stage 1 and 2 tumors (p=0.001 and p=0.018, respectively). No significant differences were observed between stages 1 and 2. Similarly, only the VAT/SAT ratio differed significantly between localized disease and systemic disease (0.65±0.43 and 0.86±0.44, respectively, p=0.023).

Conclusion: Given that body composition parameters provide a more refined assessment of obesity than body mass index and are readily available from routine CT scans, they can serve as valuable tools for tumor staging and prognostication in patients with testicular cancer.

Keywords: Chemotherapy, computed tomography, skeletal muscle area, subcutaneous adipose tissue, testicular cancer, visceral adipose tissue

Introduction

Testicular cancer is the most commonly diagnosed cancer among males aged 15-34 years (1). The most prevalent type of cancer is the seminomatous subtype, and germ cell tumors (GCTs) account for 98% of testicular cancer cases. Regardless of tumor subtype, the prognosis remains favorable, with a five-year survival rate of 99% in localized disease, specifically reported to be 96% for stage 2 and 73% for stage 3 disease (2). Diagnosis involves clinical examination, testicular ultrasound, and assessment of tumor markers. Computed tomography (CT) scan was also performed in all patients for metastasis screening. Patients with a preliminary diagnosis of testicular tumors undergo orchiectomy for pathological diagnosis and treatment. Depending on the pathological subtype and tomography findings, some patients may require adjuvant chemotherapy or radiotherapy (1).

Body fat and muscle composition measured by CT provide important information about the metabolic status of patients. Adipose tissue functions as an active secretory organ that modulates energy equilibrium, homeostasis, inflammation, insulin resistance, angiogenesis, and fat metabolism (3,4). Changes in and dysfunction of adipose tissue are commonly observed in obesity-associated diseases, including type 2 diabetes, cardiovascular disease, breast cancer, renal cancer, and colorectal cancer (3). In consideration of fat distribution, visceral adipose tissue (VAT) is associated with a greater risk of cancer than subcutaneous adipose tissue (SAT) (5). When considering VAT activity in the context of oncogenesis, it is known to secrete adipokine, proinflammatory cytokines, and growth factors (6). In contrast, studies have found that SAT is protective and associated with better prognosis for various tumors, including prostate, colorectal, and hepatocellular carcinomas (7-9).

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In addition, skeletal muscle mass status plays an important role in predicting cancer prognosis because it is directly related to sarcopenia. Chang et al. (10) identified skeletal muscle status as an important factor in patients with hepatocellular carcinoma. Their study also showed that low skeletal muscle mass might predict relevant outcomes, with a significantly heightened risk of all-cause mortality in patients with hepatocellular carcinoma (hazard ratio: 2.04, 95% confidence interval: 1.74-2.38 (10).

The existing literature on the relationship between testicular cancer and body composition predominantly focused on changes in patients receiving adjuvant chemotherapy. During or after chemotherapy, changes in fat tissue and skeletal muscle area (SMA) directly result from the effects of chemotherapeutic agents, treatment-related inactivity, altered dietary habits, and hormonal changes (11). Previous studies have demonstrated that testicular cancer survivors often exhibit increased VAT and decreased SMA following cancer treatment (12,13). A previous study reported that treatment for testicular cancer could result in an increase in VAT and a reduction in SMA due to androgen deficiency and increased luteinizing hormone levels after treatment, which are also associated with poor prognosis and higher morbidity (12).

Although previous research has examined the relationship between adjuvant chemotherapy administered for testicular cancer and body fat distribution, the current study is the first to investigate the association between the initial tumor stage and aggressiveness. The purpose of this study was to examine the correlation between VAT, SAT, and SMA ratios and cancer stage in patients diagnosed with testicular cancer.

Methods

The Research Ethics Committee of University of Healrh Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital approved this study (approval number: 2011-KAEK-25 2023/11-06, date: 01.11.2023).

During the period from January 2018 to December 2023, 94 patients who received orchiectomy treatment at the urology clinic with a preliminary diagnosis of testicular cancer and whose pathology revealed germ cell testicular cancer were retrospectively analyzed. TNM staging was performed according to pathology results, postoperative basal tumor marker levels, and radiological examination findings.

Patients with missing tumor markers and pathology results, missing CT images, or diagnoses other than testicular cancer, those with non-germ cell subtypes, and those with extensive subcutaneous edema or intra-abdominal fluid, which could hinder the calculation of adipose volume, were not included.

Examination of CT Scans

A 128-slice multi-detector-row CT scanner (Toshiba Aquilion, Japan) was used for abdominal CT images with the following parameters: automatic tube current modulation (120 kV for tube voltage and 100-300 mAs for tube current), rotation time of 0.5 s, and table speed of 1.5-2 mm/rotation. Contrast-enhanced, thin-slice abdominopelvic CT images and a soft tissue window acquired prior to surgery were used. The SMA, VAT, and SAT of axial sections passing through the L3 vertebra plane were measured. Subsequently, the VAT/SAT, SMA/VAT, and SMA/SAT ratios were calculated. Body composition parameters were measured on CT images at the time of diagnosis before patients received any adjuvant treatment (chemotherapy or radiotherapy), thus reducing the confounding effect of chemotherapy agents on muscle breakdown. Previous studies have demonstrated that the SMA obtained passing through the L3 vertebral level is related to the total body muscle mass (14). Automatic segmentation with density adjustments was executed by utilizing the OsiriX software system (Figure 1). The Hounsfield unit (HU) cut-off values were defined as 150 to 50 HU for VAT and 190 to 30 HU for SAT. The measurements were undertaken by two radiologists.

Statistical Analysis

We used SPSS v. 25 (SPSS Inc., Chicago, IL) for statistical analyses. We assessed the normality of the data distribution using the Shapiro-Wilk test. Numerical variables were presented as mean ± standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data. We conducted statistical analyses using Student's t-test for normally distributed data and the Mann-Whitney U test for data not following a normal distribution. Categorical variables were reported as counts and percentages and compared using the chi-square test. The receiver operator characteristic (ROC) curve analysis was conducted on the VAT/SAT ratio to differentiate between local and systemic diseases. A p-value 0.05 was considered statistically significant.

Results

A total of 94 patients, with a mean age of 35.05±10.44 years, who underwent surgery for testicular cancer participated in this study. Among them, 58 (61.7%) had seminomatous GCTs and 36 (38.3%) had non-seminomatous GCTs. After radiological and biochemical examination, 51 (54.3%) patients were classified as stage 1, 37 (39.4%) as stage 2, and six (6.4%) as stage 3. There was no difference in the stage distribution between patients with and without seminomatous GCTs (p=0.177). The distribution of patients according to tumor stage is shown in Figure 2.

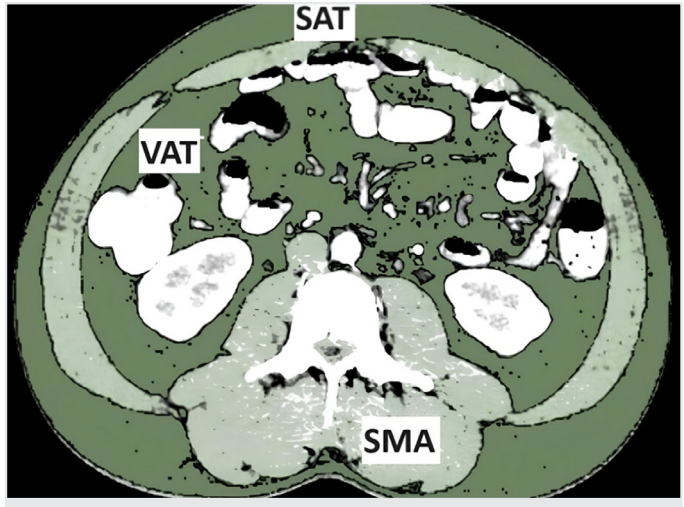

Figure 1. Axial computed tomography scan at the level of the third lumbar vertebrae in a patient with testicular cancer. Skeletal muscle area, visceral adipose tissue, and subcutaneous adipose tissue were measured semi-automatically using OsiriX software
SAT: Subcutaneous adipose tissue, VAT: Visceral adipose tissue, SMA: Skeletal muscle area

The mean tumor size was 46.8±25.3 (5-130) mm. Forty (42.6%) patients received adjuvant chemotherapy with carboplatin or bleomycin, etoposide, or cisplatin following surgery. During follow-up, 5 (5.3%) patients died, and 89 survived.

The adipose tissue composition, as measured by CT in patients with seminomatous and non-seminomatous GCTs, is presented in Table 1. Since there was no difference among the groups according to the calculated compositions and ratios, it was assumed that fat compositions were not affected by the tumor's pathological subtype in the study cohort. A moderate positive correlation was observed between tumor stage and the VAT/SAT ratio (r=0.35, p=0.001). The mean VAT/SAT ratio was 0.64±0.43 for stage 1 tumors, 0.81±0.41 for stage 2 tumors, and 1.32±0.29 for stage 3 tumors, indicating remarkable differences among the groups (p=0.001). Comparisons of the stage groups revealed that the VAT/SAT ratio was considerably higher in stage 3 than in stage 1 and 2 tumors (p=0.001 and p=0.018, respectively). There were no remarkable differences among stages 1 and 2. Similarly, only the VAT/SAT ratio differed significantly between localized disease and systemic disease (0.65±0.43 and 0.86±0.44, respectively, p=0.023). Figure 3 shows the ROC curve analysis for the VAT/SAT ratio in discriminating between local and systemic diseases at diagnosis. A VAT/SAT ratio >0.84 was able to discriminate systemic disease with a sensitivity of 55.5%, specificity of 79.6%, and area under the curve value of 0.663 (0.558-0.757).

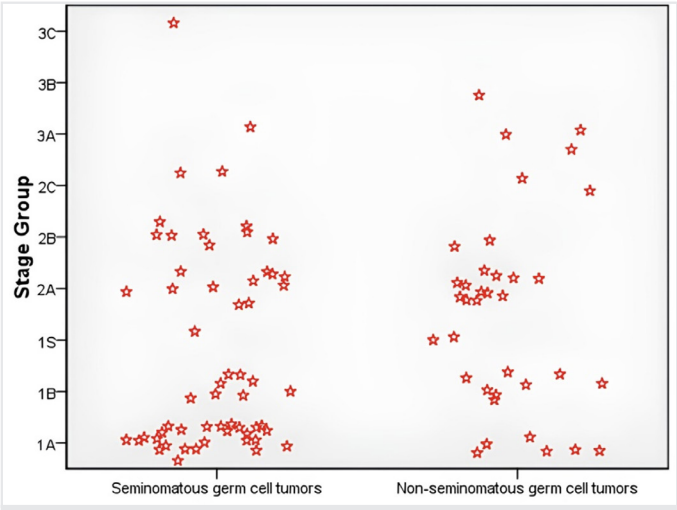

Figure 2. Distribution of seminomatous and non-seminomatous germ cell tumors by tumor stage

Table 1. Distribution of body fat composition of seminomatous and non-seminomatous germ cell tumors

	Seminomatous GCT	Non-seminomatous GCT	p
VAT (cm^2)	96±64.8	90.2±72.7	0.686
SAT (cm^2)	143.3±87.1	117±68.8	0.128
SMA (cm^2)	140.4±26.4	136.2±24	0.436
VAT/SAT	0.73±0.42	0.77±0.48	0.677
SMA/SAT	1.74±2.5	1.7±1.16	0.922
SMA/VAT	2.92±3	2.94±2.52	0.946

GCT: Germ cell tumor, VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, SMA: Skeletal muscle area

Tumor size and body fat composition were negatively correlated with SAT and SMA at moderate and low levels, respectively (r=-0.357, p<0.001 and r=-0.254, p=0.014, respectively). A positive moderate correlation was found between tumor size and the VAT/SAT and SMA/SAT ratios (r=0.334, p=0.001 and r=0.362, p<0.001, respectively). Only the SAT differed according to mortality status. The mean SAT values were 59.7±19.7 in patients who died and 137.4±81.4 in those who survived (p<0.001). No statistically significant differences were observed for the other measurements.

Discussion

Adipose tissue acts as an active secretory organ, modulating energy equilibrium, homeostasis, insulin resistance, and angiogenesis (3). It is well known that obesity is a pro-tumorigenic factor that may facilitate tumor development. The main inflammatory pathways are activated by adipose tissue products, initiating a series of mechanisms involving proliferation, invasion, and angiogenesis (15). In a study including 40 patients with breast cancer and a control group of 40 individuals, Schapira et al. (16) reported that individuals with visceral obesity possessed a considerably higher propensity for breast cancer compared with the control group. Similarly, in a meta-analysis examining the relationship between CRC and obesity, Dong et al. (17) identified a positive correlation between central obesity and CRC. Central obesity had the highest accuracy in predicting the risk of cancer development among the different types of obesity (17). Many mechanisms remain to be further elucidated to determine the association between central obesity and cancer development. In a study investigating the association between lung cancer and visceral obesity conducted by Hidayat et al. (18), every 10 cm increase in abdominal circumference was associated with a 10% higher propensity for lung cancer. However, cancer risk

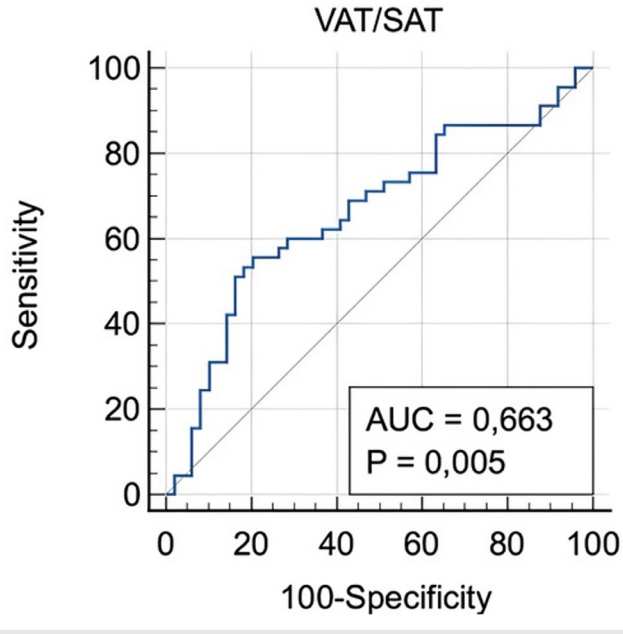

Figure 3. Receiver operating characteristic curve of the VAT/SAT ratio for discriminating between localized and systemic disease
VAT: Visceral adipose tissue, SAT: Subcutaneous adipose tissue, AUC: Area under the curve

was unrelated to body mass index (BMI), further indicating the greater importance of central obesity in cancer development (18). The assessment of body composition via CT is a comprehensive method that provides more detailed information than BMI calculation. CT allows for the separate calculation of parameters constituting body composition, namely SAT, VAT, and SMA. Moreover, it can be employed as a standard technique during follow-up.

In this study, although VAT, SAT, and SMA values alone did not show statistically significant differences, the VAT/SAT ratio increased as the stage progressed in patients with testicular cancer. Moreover, a VAT/SAT ratio >0.84 was found to indicate systemic disease, with a sensitivity of 55.5% and specificity of 79.6%.

Despite numerous studies investigating the association between central obesity and cancers such as colon, breast, and endometrial cancer, there is insufficient research on the association between testicular cancer and central obesity (3,6,17). This may be due to the younger age of patients with testicular cancer, who typically exhibit less pronounced changes in body composition. Additionally, the reduction in muscle mass in young men is likely to be less significant than that in elderly individuals with cancer. Similarly, cancer cachexia, a condition commonly expected in elderly individuals with cancer, involves a decrease in muscle mass due to age, inactivity, and cancer development. However, in testicular cancer patients, who are typically young males, the decline in muscle mass is not as pronounced as in other types of cancer, which could explain why the body compositions analyzed in our study did not change significantly. The analysis of composition ratios revealed that VAT/SAT was correlated with tumor stage and systemic disease spread, which may be related to the active role of VAT in cytokine production.

The correlation between SAT and cancer-related mortality has been investigated in only few studies. A recent study of 1,746 patients with gastrointestinal, respiratory, or renal cancer definitively established that a low SAT was strongly correlated with poor survival outcomes (19). In a study of 3,324 patients, cancer-related mortality was associated with increased VAT and SAT values (20). Similarly, SAT was significantly lower in patients with testicular cancer-related mortality in our study (59.7±19.7 and 137.4±81.4, respectively).

Considering the association between survival and body composition, no statistically significant relationship was detected. This may be attributed to the high survival rates of patients with testicular cancer and the relatively low occurrence of complications during treatment.

Study Limitations

The main limitation of this study was the lack of information about the dietary patterns and activity levels of the patients. The current study only assessed radiological fat composition upon diagnosis.

Conclusion

This study demonstrated that fat composition parameters measured by CT provide a more accurate assessment of obesity than BMI. Additionally, these parameters can be utilized to evaluate cancer stage and prognosis in patients with testicular cancer.

Ethics

Ethics Committee Approval: The Research Ethics Committee of University of Healrh Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital approved this study (approval number: 2011-KAEK-25 2023/11-06, date: 01.11.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - D.B., A.E.; Concept - S.G.G.Ö., M.E.; Design - S.G.G.Ö., A.E.; Data Collection or Processing - S.G.G.Ö., D.B.; Analysis or Interpretation - S.G.G.Ö.; Literature Search - S.G.G.Ö.; Writing - S.G.G.Ö., M.E., A.E.

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

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Impact of Drain Use and Tourniquet Release Timing on Blood Loss, Operative Time, and Wound Complications in Total Knee Arthroplasty

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ABSTRACT

Introduction: This study aimed to investigate the effects of different practices regarding tourniquet release timing and drain usage in primary total knee arthroplasty (TKA) on intraoperative and post-operative blood loss, operative time, and post-operative complications.

Methods: A retrospective review was conducted on the records of patients who underwent TKA by one of four authors (E.Ö., S.Y., F.E.M., S.A.A.) from 01.09.2023 to 01.11.2024. Patients were divided into three groups: group A, early tourniquet release without drain use (E.Ö.); group B, early tourniquet release with drain use (F.E.M.); group C, late tourniquet release with drain use (S.A.A. and S.Y.). Patients with revision TKAs or use of constrained prosthesis, or removal of hardware were excluded. A total of 102 patients were identified. Demographic, blood loss, and operative time data were collected. The groups were compared regarding changes in pre- and post-operative hemoglobin (Hb) levels, operative times, and post-operative complications.

Results: No significant differences in age, gender distribution, or pre-operative and post-operative Hb levels were observed between the groups ($p>0.05$). All groups showed a significant decrease in post-operative Hb levels compared with pre-operative values ($p<0.05$), but the Hb change was not statistically different between groups ($p>0.05$). The operative time was significantly longer in group B (122.0±18.6 minutes) than in groups A (101.0±14.3 minutes) and C (97.6±21.5 minutes) ($p<0.05$). Wound complications included prolonged wound drainage in group A, acute infection in group B, and superficial infection in group C, with no significant differences in complication rates between groups ($p>0.05$).

Conclusion: Our results showed that different tourniquet release timings and drain use did not significantly impact perioperative blood loss but may affect the operative time. Specifically, drain use and early tourniquet release were associated with longer operation times. These findings suggest that late tourniquet release minimizes the operative time while maintaining comparable blood loss. This approach may be particularly beneficial in busy surgical settings where reducing operative time is a priority, without compromising patient safety or clinical outcomes.

Keywords: Arthroplasty, drainage, tourniquet, blood loss

Introduction

Osteoarthritis (OA) is a common disability that affects millions of people around the world (1). Severe OA of the knee is treated with total knee arthroplasty (TKA), which is a frequently performed procedure. More than 700,000 TKAs are performed each year worldwide (2). Although the technique is mostly standard and well-established, there are differences in practice exist between surgeons regarding various aspects of the pre-, per-, and post-operative applications.

Drain use is a routine practice in primary TKA (3). In fact, all orthopedic surgeons in the present study were trained in institutions where drain use was the routine practice in all TKAs.

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Another controversial topic in primary TKA is the early release of tourniquets. Early release refers to obtaining hemostatic control before closing the fascial incision by releasing a tourniquet after hardening of the cement. Late release refers to the release of the tourniquet after skin closure.

In our institution, the authors of the present study follow different practices. EO practices early tourniquet release without drain use, F.E.M. practices early tourniquet release with drain use, and S.A.A. and S.Y. practice late tourniquet release with drain use. A considerable number of studies have compared tourniquet and drain practices (4). However, to our knowledge, no studies have compared combinations of these practices side by side. Understanding this issue may help optimize surgical protocols, especially in busy hospitals where efficiency and patient outcomes are crucial. By comparing these combinations side by side, this study aims to fill a critical gap in the existing literature. The present study investigated the effect of drain use and hemostasis on intra- and post-operative blood loss, operation time, and wound complications.

Methods

The University of Health Sciences Türkiye, İstanbul Physical Therapy and Rehabilitation Training and Research Hospital, Ethical Committee approved the study (approval number: 2024-64, date: 08.10.2024). Records of patients who had TKA by one of the four authors (E.Ö., S.Y., F.E.M., and S.A.A.) between 01.09.2023 and 01.11.2024 were retrospectively reviewed. Revision TKAs, primary TKAs in which a condylar constrained prosthesis was used, and primary TKAs involving the removal of previous hardware were excluded. A total of 102 patients were identified. All authors used tourniquet and 1 g of intraoperative intravenous tranexamic acid (TXA). Demographic information was obtained from the hospital records system, whereas blood loss and operation time data were obtained from the anesthesia records. The baseline characteristics and surgical details of the study population are summarized in Table 1.

Group A consisted of patients who were operated solely by one of the authors (E.Ö.), who practices early tourniquet release without drain use.

Tablo 1. Baseline characteristics and surgical details of the study population

	Minimum-maximum	Median	Average ± SD/(n, %)
Age	53.0-81.0	69.0	68.9±6.6
Sex			
Male			16 (15.6%)
Female			86 (84.3%)
Hemoglobin	10.3-16.6	13.1	13.0±1.2
Operation time	65.0-150.0	105.0	104.9±20.6
Groups			
A			32 (31.3%)
B			24 (23.6%)
C			46 (45.1%)

SD: Standard deviation

Group B consisted of patients who were operated solely by another author (F.E.M.), who practices early tourniquet release with drain use. Group C consisted of patients operated by S.A.A. and S.Y., who practice late tourniquet release with drain use.

Surgical Pocedure

All patients underwent cemented TKA using TIPMED primary total knee implants (TIPMED, İzmir, Türkiye) (Figure 1). All patients received combined spinal and epidural anesthesia. TKA was performed by midline skin incision and medial parapatellar arthrotomy under a pneumatic tourniquet. For bony resection, an intramedullary alignment system was used for the femur, with an extramedullary device for the tibia. None of the patients underwent patellar resurfacing. The intramedullary guide holes in the distal femur were plugged with autologous bone grafts from distal femoral cuts in each patient before inserting the components.

In group A, the tourniquet was deflated when the cement had hardened; then, homeostasis was attempted. No drains were used. In group B, the tourniquet was deflated when the cement had hardened; then, homeostasis was attempted. Drains were used in each case. In group C, drains were used for each patient. The fascial layer, subcutaneous tissue, and skin were then closed, the tourniquet was deflated after closing the wound, and a compressive dressing was applied. A compressive bandage was applied using a layer of cotton wool and two layers of elastic bandage in all groups.

Statistical Analysis

The mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Simirnov and Shapiro-Wilk tests. ANOVA (Tukey's test) was used in the analysis of quantitatively independent data with normal distribution. The Kruskal-Wallis and Mann-Whitney U tests were used in the analysis of quantitative independent data with abnormal distribution. The Paired Samples t-test was used in the analysis of dependent quantitative data. The chi-square test was used in the analysis of qualitatively independent data, and the Fisher's exact test was used when the chi-square test conditions were not met. The Spearman Correlation Analysis was used in the correlation analysis, and the SPSS 27.0 (IBM, Chicago, IL, USA) program was used in the analysis.

Results

There were no significant differences in the age of patients between groups A, B, and C (69.6±6.6, 70.4±8.4, and 68.0±5.9 years, respectively; p=0.346, Table 2). Similarly, there was no significant difference in gender distribution across the groups (p=0.465, Table 2). Males accounted for 9.4%, 16.7%, and 19.6% of groups A, B, and C, respectively, whereas females accounted for 90.6%, 83.3%, and 80.4%.

There were no significant differences between groups A, B, and C in terms of pre-operative hemoglobin (Hb) levels (12.8±1.0 g/dL, 12.9±1.0 g/dL, and 13.2±1.3 g/dL, respectively; p=0.255, Table 2). Post-operative Hb levels also did not differ significantly between the groups (11.6±1.0 g/dL, 11.0±1.2 g/dL, and 12.0±1.4 g/dL, respectively; p=0.078, Table 2). However, within each group, post-operative Hb values decreased

Tablo 2. Statistical comparison of demographic and clinical parameters among groups A, B, and C

			Group A (n=32)[1]	Group B (n=24)[2]	Group C (n=46)[3]	p
Age	Average ± SD		69.6±6.6	70.4±8.4	68.0±5.9	0.346[K]
	Median		69.5	74.5	69.0	
Sex	Male	n, %	3 (9.4%)	4 (16.7%)	9 (19.6%)	0.465X[2]
	Female	n, %	29 (90.6%)	20 (83.3%)	37 (80.4%)	
Hemoglobin						
Pre-op	Average ± SD		12.8±1.0	12.9±1.0	13.2±1.3	0.255[A]
	Median		12.6	12.7	13.3	
Post-op	Average ± SD		11.6±1.0	11.0±1.2	12.0±1.4	0.078[A]
	Median		11.6	11.2	12.3	
Pre-op/post-op değişim	Average ± SD		-1.2±0.5	-1.8±0.8	-1.3±0.7	0.094[A]
	Median		-1.2	-1.9	-1.2	
Intra-group change p-value			**<0.001[E]**	**0.001[E]**	**<0.001[E]**	
Operation time	Average ± SD		101.0±14.3	122.0±18.6	97.6±21.5	**<0.001[K]**
	Median		102.5[2]	124.5	91.0[2,1]	

[A]ANOVA, [K]Kruskal-Wallis (Mann-Whitney U test), [E]Paired t-test, X[2]Chi-square test (Fisher); [1]Difference with group A p>0.05; [2]Difference with group B p<0.05, SD: Standard deviation, Pre-op: Pre-operative, Post-op: Post-operative

significantly compared with pre-operative values: in group A, from 12.8±1.0 to 11.6±1.0 g/dL (p<0.001); in group B, from 12.9±1.0 to 11.0±1.2 g/dL (p=0.001); and in group C, from 13.2±1.3 to 12.0±1.4 g/dL (p<0.001). Despite these decreases, the magnitude of pre-operative-to-post-operative Hb changes did not differ significantly among the groups (-1.2±0.5 g/dL, -1.8±0.8 g/dL, and -1.3±0.7 g/dL for groups A, B, and C, respectively; p=0.094, Table 2).

The duration of operation was significantly different between the groups (p<0.001, Table 2). Group B had the longest mean duration (122.0±18.6 minutes), followed by group A (101.0±14.3 minutes) and group C (97.6±21.5 minutes). Pairwise comparisons showed that the operation time in group B was significantly higher than that in groups A (p<0.05) and C (p<0.05), while the operation time in group A was not significantly higher than in group C (p>0.05). Results are visualized in Figure 2.

No significant correlations were observed between the magnitude of Hb changes and patient age or the duration of surgery (p>0.05, Table 3).

Wound complications included one case of prolonged wound drainage in group A, treated with wound care, one case of acute periprosthetic infection in group B requiring debridement, antibiotics, and polyethylene exchange (Figure 3), and one case of superficial wound infection in group C requiring surgical debridement. The results did not significantly differ between the groups (p>0.05). There were no cases of deep vein thrombosis.

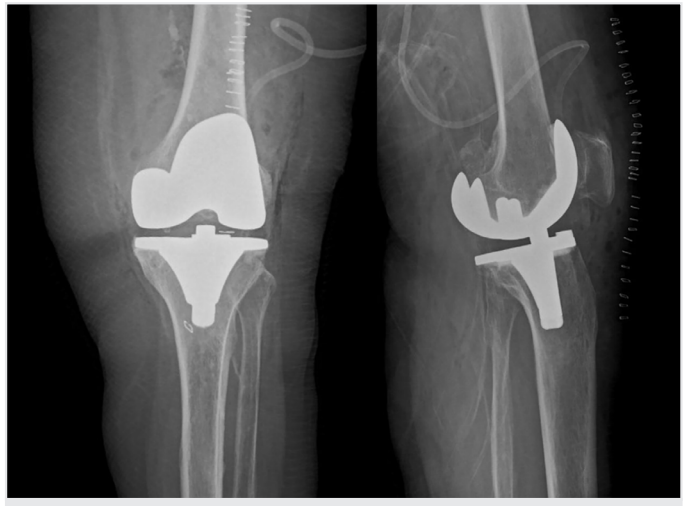

Figure 1. Anteroposterior and lateral X-rays of a TIPMED primary cruciate-retaining total knee arthroplasty

Tablo 3. Spearman correlation between hemoglobin change, age, and operation time

		Age	Operation time
Hemoglobin change	r*	-0.198	0.050
	p**	0.065	0.644

*Correlation coefficient, **p-value

Discussion

Literature suggests that while drains are traditionally used to manage post-operative hematoma, they may contribute to a significant decrease in hematocrit (Hct) levels, increased blood loss, and a higher need for transfusions, without substantial benefits. Madan et al. (5) conducted a retrospective review of 152 patients and found that drain use was linked to greater Hct reductions (p=0.002) and higher transfusion needs (p=0.044). Similarly, Albasha et al. (6) observed that patients with drains had more pronounced Hct drops and longer hospital stays (p<0.05), and Ares et al. (7) reported that drained volume correlated with further reductions in Hct, suggesting ongoing blood loss related to drain placement. There are also studies, such as one by Manta et al. (8), who found that while use of drains did not increase blood loss or transfusion rates, no difference in knee swelling was found between groups, questioning the benefit of using drains at all.

One theoretical benefit of drain use is preventing hematoma formation, resulting in decreased wound complications, which in turn translate

to lower infection rates. However, previous studies have found no difference in infection rates between patients with or without drain use (9,10). In a 2016 meta-analysis by Si et al. (11), 12 randomized controlled trials consisting of 889 TKAs examined the effects of closed drainage compared with non-drainage after TKA. The analysis found no notable difference in infection rates between the groups, although drain use was linked to an increased need for blood transfusions and extended hospital stays (11). This raises the question of whether avoiding or modifying drain usage might be beneficial for patients undergoing TKA.

The use of tourniquets is another controversial topic in TKA, as previous studies have reported mixed outcomes. Although tourniquets reduce intraoperative blood loss, they do not significantly impact total blood loss. Meta-analyses by Tai et al. (12) and Zhang et al. (13) showed that tourniquets lower measured blood loss during surgery but not overall, with associated increases in complications like thrombosis. Research by Tan et al. (14) and others found no significant benefits in blood loss, stability, or pain relief with tourniquets, and Migliorini et al. (15) observed better functional outcomes and fewer DVTs without them. Some studies, such as Smith and Hing (16), highlight the advantage of shorter operative times with tourniquets, but this is offset by higher risks of complications, such as DVT and early joint impairment.

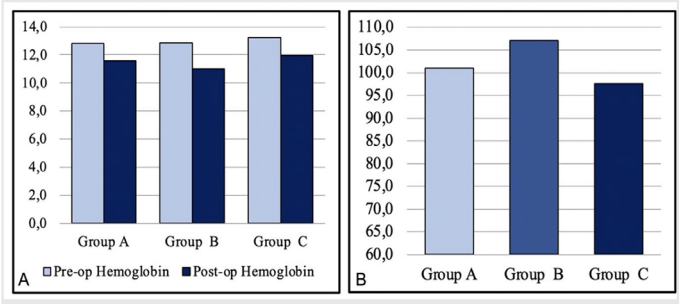

Figure 2. (A) Pre- and post-operative hemoglobin levels of groups. (B) Operation time (minutes) across groups

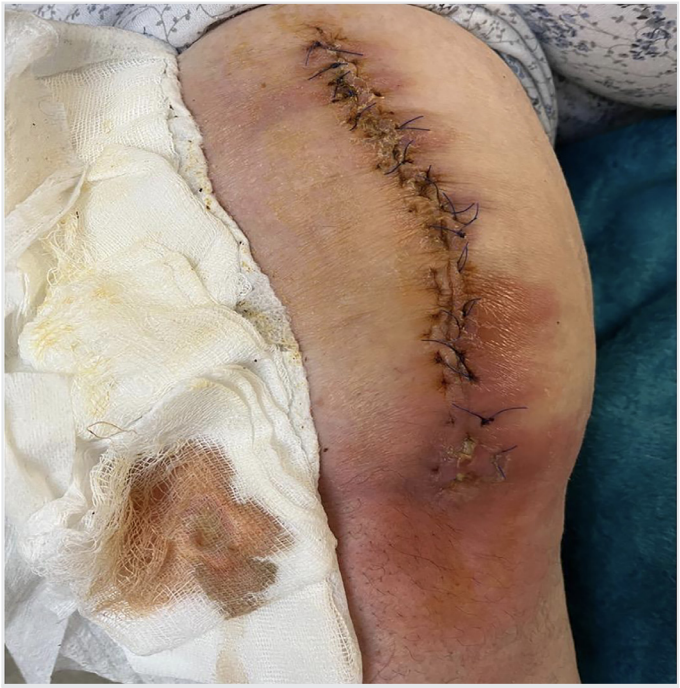

Figure 3. Persistent wound draining in a patient at post-operative week 2. The patient later underwent debridement and polyethylene exchange. Informed consent was obtained from the patient to use the image for scientific purposes

All authors in the present study used tourniquets for all patients; however, the timing of tourniquet release and hemostasis control were different. The literature is also controversial on this matter as well. Two meta-analyses by Huang et al. (17) and Rama et al. (18) have provided evidence that early tourniquet release can lead to significantly higher blood loss in TKA procedures, whereas late release post-wound closure, particularly with controlled pressure and limited duration, may mitigate this effect. Huang et al.'s (17) analysis of 14 RCTs found that late tourniquet release reduces blood loss without increasing the risk of complications, and Rama et al.'s (18) meta-analysis of 893 TKAs similarly noted a substantial increase in blood loss with early release. Our findings are consistent with the results of these studies.

Additional studies, including those by Velyvis (19), Yildiz et al. (20), and Demirkale et al. (21), support the strategic combination of tourniquet timing with hemostatic measures to optimize outcomes. Yildiz et al. (20) conducted a retrospective analysis and found that tourniquet release after skin closure, paired with drain clamping, effectively reduced blood loss without added complications, whereas Demirkale et al. (21) noted reduced infection rates with late release in non-drainage protocols. Chang et al. (22) further illustrated that releasing the tourniquet post-arthrotomy closure decreased ischemia time, improved early recovery, and had no adverse effects on complications. Collectively, these findings suggest that late tourniquet release, particularly when paired with additional hemostatic strategies, may provide a safer and more effective approach in TKA.

Prolonged procedures may increase surgical complications (23). The shortest possible operative time should be planned without compromising the technical quality and exposing the patient to unnecessary risks. Our results indicate that there are no differences between drain use and early tourniquet release in terms of peroperative blood loss, whereas both contribute to increased operation times. The present study's findings regarding drain use in TKA align with other research, suggesting limited benefits and potential drawbacks. For example, Albasha et al. (6) found that drains were associated with longer hospital stays, increased blood loss, and higher transfusion rates compared with cases without drains. Similar to the current study, their results suggest that although drains may theoretically control hematoma formation, they may actually increase blood loss due to continued post-operative bleeding. Furthermore, unlike other studies that emphasize higher transfusion requirements with drain use, our study did not show significant differences in perioperative blood loss across groups, regardless of drain usage or tourniquet timing. This finding could be attributed to the standardized use of TXA, a factor that Albasha et al. (6) highlighted as significantly improving post-operative outcomes when used with or without drains.

Study Limitations

The study has several limitations. First, the retrospective study design inherently limits the ability to control for confounding factors, which

may impact the results. Second, the sample size is relatively small, particularly in group B, which could affect the statistical power of the findings and the generalizability of the results. Another limitation of the present study was that only early post-operative Hb levels were assessed. Post-operative Hb levels were not routinely monitored because this is not standard practice in our institution. This limitation restricts the ability to fully evaluate long-term trends in blood loss or potential delayed anemia, which could provide additional insights into the effects of different tourniquet and drain practices over time. Other factors not included in this study, such as body mass index, patient comorbidities, and surgeon variability, may have also influenced the results.

Conclusion

Our results indicate that although there were no significant differences in perioperative blood loss between the groups, the use of drains and early tourniquet release were associated with longer operative times. Late tourniquet release resulted in shorter operation times without compromising perioperative blood loss or increasing wound complications. These findings suggest that adopting late tourniquet release as a standard practice in TKA may improve surgical efficiency, particularly in high-volume surgical centers, while maintaining patient safety and clinical outcomes.

Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, İstanbul Physical Therapy and Rehabilitation Training and Research Hospital, Ethical Committee approved the study (approval number: 2024-64, date: 08.10.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - E.Ö., F.E.M., S.A.A., K.Y.K., B.A., S.Y.; Concept - E.Ö., A.B., B.A., K.Y.K., S.Y.; Design - E.Ö., M.Y.G., K.Y.K., B.A., S.Y.; Data Collection or Processing - E.Ö., M.Y.G.; Analysis or Interpretation - E.Ö., A.B., F.E.M., S.A.A.; Literature Search - E.Ö., A.B., F.E.M., S.A.A.; Writing - E.Ö., M.Y.G.

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Assessing Diagnosis, Demographics, and Medication Compliance in Elderly Patients with Rheumatic Disease

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ABSTRACT

Introduction: This study aimed to evaluate the diagnostic distribution, demographic characteristics, and medication adherence of elderly patients with rheumatic diseases (RD) and to contribute to improving adherence rates and patient outcomes in this demographic group by examining the factors affecting treatment adherence.

Methods: This cross-sectional observational study included 108 patients aged >65 years diagnosed with RD. Data on demographic characteristics, disease characteristics, comorbidities, and medication use were collected. Medication adherence was assessed using the Morisky Medication Adherence Scale-8 and the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression levels.

Results: The median age of the participants was 70.5 years, with 69.4% female predominance. The most common diagnoses were rheumatoid arthritis (41.67%), gout (14.81%), and polymyalgia rheumatica (11.11%). Good adherence was associated with higher social support [odds ratio (OR): 4.99, 95% confidence interval (CI): 1.45-17.11], lower medication count (OR: 0.78, 95% CI: 0.63-0.95), and lower HADS scores (OR: 0.93, 95% CI: 0.87-0.98). Forgetfulness was the leading cause of non-adherence, as reported by 40.7% of patients.

Conclusion: This study highlights that social support, polypharmacy, and mental health significantly affect medication adherence in elderly patients with RD. Medication adherence remains an important factor in the effective management of RD, and demographic factors, such as comorbidities and socioeconomic status, play influential roles.

Keywords: Elderly rheumatic disease, medication compliance, the Morisky Medication Adherence Scale, the Hospital Anxiety and Depression Scale

Introduction

Rheumatic disorders are an important health problem in the elderly population. Among musculoskeletal problems, degenerative joint diseases, osteoporosis, and soft tissue rheumatism are common in the geriatric population in general, whereas rheumatic diseases (RD) include rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), and crystalline arthropathies. It is also well known that the highest incidence of several types of inflammatory RD, including PMR, giant cell arteritis, and remitting seronegative symmetric synovitis with pitting edema, is highest in the elderly (1,2). RD significantly affects the quality of life and functional capacity of this population. The unique physiological and psychosocial aspects of aging should be considered when managing these conditions. Effective management requires a multifaceted treatment approach including pharmacological interventions, physical therapy, and lifestyle modification (3).

The increasing incidence of chronic diseases with aging is a natural consequence of the dramatic increase in medication use (4). Treatment adherence in geriatric patients presents unique challenges due to factors such as cognitive decline with polypharmacy, physical limitations, and socioeconomic constraints. Understanding and improving adherence in this context is vital for improving therapeutic outcomes and enhancing patient well-being (2,5).

In this article, we aim to evaluate the demographic data, diagnostic distribution, and treatment adherence of geriatric rheumatological patients, as well as to identify factors influencing treatment adherence and provide actionable recommendations to improve adherence.

Methods

Between October 2019 and December 2022, patients over the age of 65 with a diagnosis of RD treated in the rheumatology outpatient clinic

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of our hospital were consecutively included in this cross-sectional-observational study without any exclusion criteria. Informed consent was obtained from patients who agreed to participate in the study and who were assured that they would be fully informed about the evaluation methods and the aims of the study. Physical examinations were performed to determine the clinical characteristics of the patients, and patient files were retrospectively analyzed for the results of the tests. The following information was recorded: age, gender, rheumatological disease, educational status, socioeconomic status, smoking, comorbidities, all medications used, disease onset date, all medications used, and duration of use. To assess treatment compliance, the Morisky Medication Adherence Scale (MMAS-8) and the Hospital Anxiety and Depression Scale (HADS) was utilized to assess anxiety and depression.

MMAS-8, an eight-item scale developed from a previously validated four-item scale, is a structured self-report measure of medication-taking behavior (6,7). This study was designed to facilitate the recognition of barriers and behaviors associated with adherence to medications requiring chronic use, such as RD. The scale provides information about patient behaviors related to medication adherence that may be involuntary, such as forgetfulness, or voluntary, such as not taking medication due to side effects. The first seven questions are dichotomized and the last question 8 is a 5-point Likert Scale. Question 8 is a 5-point Likert Scale that assesses the frequency with which patients forget their medication, ranging from zero to one in 0.25-point increments (never: 1, sometimes: 0.75, sometimes: 0.5, usually: 0.25, and always: 0). The total score is the sum of all MMAS-8 items and ranges from 0 to 8, with 8 reflecting high adherence, 7-6 reflecting moderate adherence, and <6 reflecting low adherence. Turkish validity and reliability were assessed (8).

The HADS is a self-reported scale consisting of 14 questions measuring anxiety and depression. All questions were scored from 0 (no impairment) to 3 (severe impairment) and 0-7 points are considered normal, 8-10 points are considered borderline, and 11 and above were considered abnormal (9).

Before the study was conducted, ethics committee approval was obtained from Marmara University Faculty of Medicine Research Ethics Committee (approval number: 09.2019.1079, date: 06.12.2019). The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The SPSS 26 package program was used to analyze the data. Shapiro-Wilk test was used to determine whether the data were normally distributed. While numbers and percentages were used for categorical variables, median [25% (Q1) - 75% (Q3) quartiles] was used for continuous variables. For the comparison of categorical variables, the chi-square test was used, and for the comparison of continuous variables, Mann-Whitney U test was used. To determine independent predictors of good adherence, potential variables identified in univariate analyses were included in multivariate logistic regression (LR) analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Statistical significance was taken as $p<0.05$.

Results

A total of 108 elderly patients diagnosed with rheumatologic diseases and taking medication were included in the study. The median age of the patients was 70.5 years (67.0-75.7) and 69.4% (n=75) were female. The distribution of rheumatologic disease diagnoses is shown in Figure 1 and the 3 most common diseases were RA (41.67%), gout (14.81%), and polemology rheumatica (11.11%). Demographic characteristics,

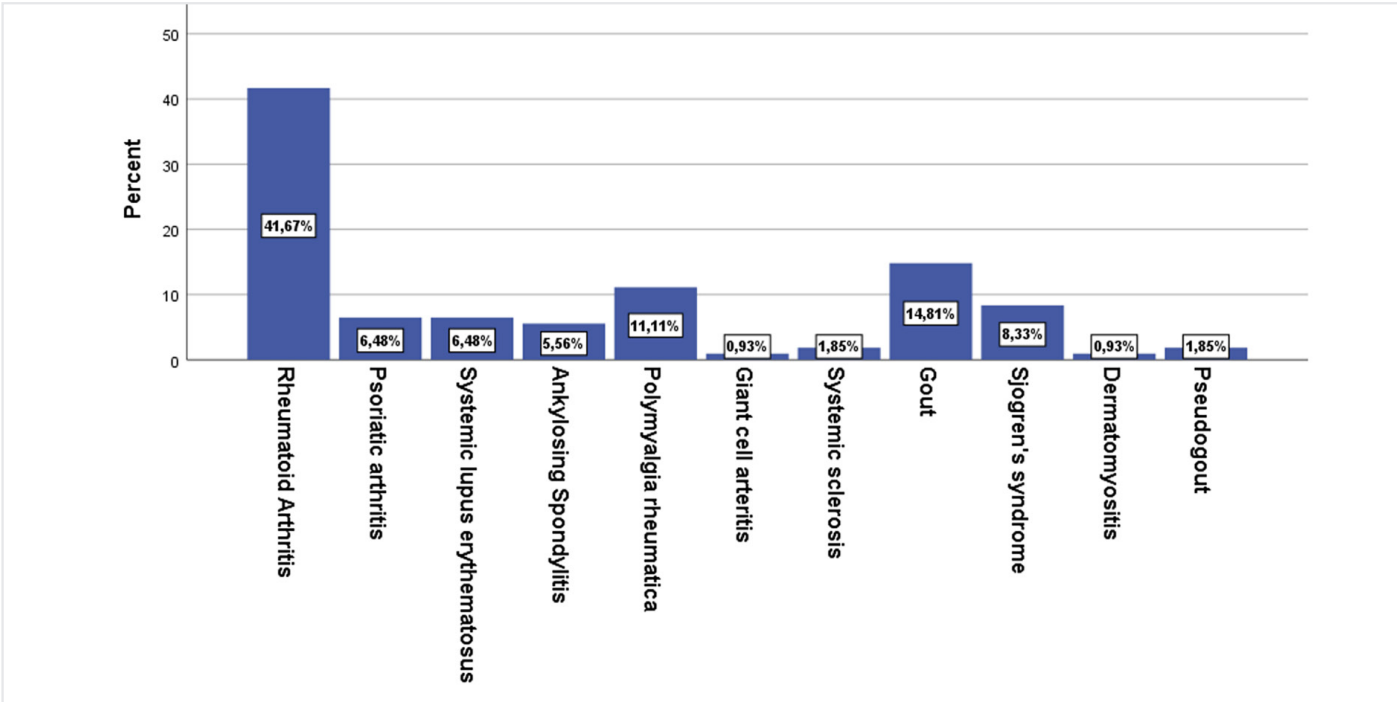

Figure 1. The distribution of rheumatologic disease diagnosis

Table 1. Demographic characteristics, comorbid diseases and medication information of the patients

	No. (n=108)	Percentage/ median [25% (Q1)-75% (Q3) quartiles]
Age, years		70.5 (67.0-75.7)
Sex		
Male	33	30.6
Female	75	69.4
Educational level		
Illiterate/primary school	68	63.0
Middle school	13	12.0
High school	9	8.3
University graduate	18	16.7
Marital status		
Married	65	60.2
Single/divorced/widowed	43	39.8
Occupation		
Employed	9	8.3
Unemployed/housewife	51	47.2
Retired	48	44.4
Social support		
Yes	92	85.2
No	16	14.8
Smoker		
Yes	16	14.8
No	92	85.2
Disease duration in months		65 (32.5-124.0)
Treatment duration in months		65 (34.2-124.7)
Number of drugs used		6 (4-8)
Presence of active disease	22	20.4
Comorbid diseases		
Hypertension	83	76.9
Diabetes mellitus	40	37.0
Coronary artery disease	33	30.6
Current medications*		
Corticosteroid	47	43.5
DMARD	85	78.7
Methotrexate	21	19.4
Leflunomide	38	35.2
Hydroxychloroquine	38	35.2
Sulphasalazine	12	11.1
Biologic durgs	6	5.6
Azathioprine	4	3.7
Colchicine	20	18.5
Mycophenolate mofetil	5	4.6
MMAS-8		7 (6-8)
HADS		11 (7-16)
Normal	30	27.8
Borderline	20	18.5
Upnormal	58	53.7
The answers of the patients to the possible reasons for medication non-adherence		
Forgetfulness	44	40.7
Insufficient information	6	5.6
Drug side effects	30	27.8
Doubt about the efficacy of medications	18	16.7
Concern about side effects	27	25.0
Cost of medicines/social support	12	11.1

*More than one medication was allowed. DMARD: Disease-modifying anti-rheumatoid drugs, MMAS-8: Morisky Medication Adherence Scale with 8 items, HADS: Hospital Anxiety and Depression Scale

comorbid diseases, and medication information of the patients are presented in Table 1. The median disease duration was 65 (32.5-124.0) months. The median number of drugs used was 6 (4-8). Patients with active disease were 20.4% (n=22). The median MMAS-8 and HADS scores were 7 (6-8) and 11 (7-16), respectively. The answers of the patients to the questions considered as possible reasons for medication non-adherence are given in the Table 1 and it was found that the most common reason was forgetfulness with 40.7% (n=44). According to the MMAS-8 questionnaire, patients who scored 7 and 8 points were divided into "good adherence" and those who scored 6 or less points were divided into "low adherence" groups. The comparison of the groups is given in Table 2 and social support was significantly higher in the good adherence group, whereas the number of medications used and HADS were significantly lower. The number of drugs used in the low and good adherence groups are given graphically in Figure 2. The variables considered influencing good adherence were included in the binary LR analysis. In the multivariable model, backward: Using the LR method, only social support (OR: 4.99, 95% CI: 1.45-17.11), number of drugs used (OR: 0.78, 95% CI: 0.63-0.95) and HADS (OR: 0.93, 95% CI: 0.87-0.98) were statistically significant and these variables are shown in Table 3.

Discussion

Rheumatological diseases are among the most important health problems faced by the elderly population. The current study focused on the diagnosis, demographic findings, and treatment compliance of rheumatological diseases in geriatric patients admitted to the rheumatology outpatient clinic. In our study, significant relationships were found between good treatment compliance, social support, the number of medications used, and anxiety and depression levels. The findings highlight the many factors affecting the treatment compliance of elderly patients and the need for a multidimensional approach to increase treatment compliance.

The demographic data from this study are consistent with previous research indicating a higher prevalence of RD in older adults, particularly in women. In a large cohort study of elderly patients with inflammatory

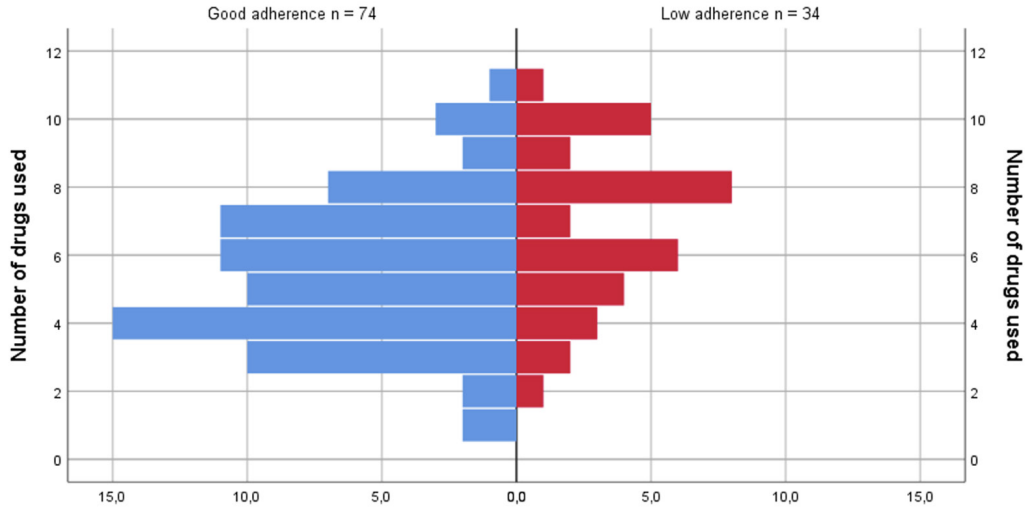

Figure 2. Graphical distribution of the number of drugs used in the low and good adherence groups

Table 2. Demographic characteristics and accompanying diseases according to medication compliance in elderly patients

	Low adherence, (n=34)	Good adherence, (n=74)	p
Age, years	71 (67-76)	70 (67-75)	0.530
Sex			
Male	14 (41.2%)	19 (25.7%)	0.104
Female	20 (58.8%)	55 (74.3%)	
Educational level			
Illiterate/primary school	23 (67.6%)	45 (60.8%)	0.428
Middle school	2 (5.9%)	11 (14.9%)	
High school	2 (5.9%)	7 (9.5%)	
University graduate	7 (20.6%)	11 (14.9%)	
Marital status			
Married	20 (58.8%)	45 (60.8%)	0.716
Single/divorced/ widowed	14 (41.2%)	29 (39.2%)	
Occupation			
Employed	3 (8.8%)	6 (8.1%)	0.690
Unemployed/ housewife	14 (41.2%)	37 (50%)	
Retired	17 (50%)	31 (41.9%)	
Social support			
Yes	24 (70.6%)	68 (91.9%)	0.004
No	10 (29.4%)	6 (8.1%)	
Smoker			
Yes	7 (20.6%)	9 (12.2%)	0.252
No	27 (79.4%)	65 (87.8%)	
Disease duration in months	63 (37-130)	65 (30-109)	0.576
Treatment duration in months	63 (36-130)	65 (30-120)	0.660
Number of drugs used	7 (5-8)	5 (4-7)	0.004
Presence of active disease	8 (23.5%)	14 (18.9%)	0.581
Comorbid diseases			
Hypertension	29 (85.3%)	54 (73%)	0.159
Diabetes mellitus	15 (44.1%)	25 (33.8%)	0.304
Coronary artery disease	14 (41.2%)	19 (25.7%)	0.109
HADS	14 (10-18)	10 (6-15)	0.012
Normal	6 (17.6%)	24 (32.4%)	0.054
Borderline	4 (11.8%)	16 (21.6%)	
Upnormal	24 (70.6%)	34 (45.9%)	
The answers of the patients to the possible reasons for medication non-adherence			
Forgetfulness	29 (85.3%)	15 (20.3%)	<0.001
Insufficient information	6 (17.6%)	0	0.001
Drug side effects	17 (50.0%)	13 (17.6%)	0.001
Doubt about the efficacy of medications	12 (35.3%)	6 (8.1%)	<0.001
Concern about side effects	19 (55.9%)	8 (10.8%)	<0.001
Cost of medicines/ social support	12 (35.3%)	0	<0.001

Values are presented as number (%) or median (interquartile range). HADS: Hospital Anxiety and Depression Scale

arthritis, 64% of 13,613 patients with RA and 57% of 1,116 patients with psoriatic arthritis (PsA) were women (10). Similarly, in a study in which rheumatological diseases were evaluated in geriatric patients, 70% of the patients were female and 30% were male (11). In our cohort, 69.4% (n=75) of patients were female, and this female predominance may be attributed to the fact that autoimmune RD tends to affect women more frequently than men, thus hormonal differences, genetic predisposition, and immune system differences between the sexes.

Table 3. The independent effects of some possible predictors in relation to good adherence according to univariate/multivariate analysis

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Social support	4,722 (1,550-14,386)	0.006	4,995 (1,458-17,110)	0.010
Number of drugs used	0.761 (0.629-0.921)	0.005	0.782 (0.639-0.958)	0.017
HADS	0.930 (0.877-0.986)	0.014	0.930 (0.874-0.989)	0.022

HADS: Hospital Anxiety and Depression Scale, OR: Odds ratio, CI: Confidence interval

The prevalence of non-inflammatory musculoskeletal diseases, such as osteoarthritis, has increased in the geriatric population. Regarding RD, RA, PMR, and crystal arthropathies are considered common in geriatric patients (12). Of the 148 geriatric patients with rheumatological diseases evaluated in the study, the highest number of patients was RA with 61, followed by 25 seronegative arthritis and 24 crystal arthritis (11). The distribution of rheumatological disease diagnoses in our study, the 3 most common diseases were RA (41.67%), gout (14.81%), and polemology rheumatica (11.11%).

Li et al. (13) showed that higher adherence to medical treatment in patients with RA was associated with lower disease activity. Similarly, in patients with gout, of whom approximately one-seventh constitute our study population, there is a statistically significant relationship between medication adherence and achievement of treatment goals (14). Therefore, patient adherence to treatment is of paramount importance in the management of RD. Assessing patient adherence to treatment and implementing necessary interventions to increase adherence rates are also crucial in achieving treatment success.

RD is a chronic illness that requires long-term monitoring and often requires the use of multiple medications. They present various medical, social, and economic challenges for patients. In particular, psychological issues, such as depression and anxiety, are more frequently observed in these patients than in the general population (15). Indeed, psychosocial interventions have been shown to have positive effects during the treatment of patients with RA (16). In addition to the positive effects of social support on treatment, one of the most notable findings of our study is that it also enhances patient adherence to treatment.

Polypharmacy is associated with clinical outcomes in patients with RA. As the number of medications used increases, both the rate of side effects and the response to treatment diminishes (17). Additionally, polypharmacy has been found to be associated with disease activity in patients with rheumatoid and PsA (18). Within the scope of RD, polypharmacy occurs at varying rates across different clinical entities, and these rates are significant enough to be taken seriously. Given its relationship with both disease activity and clinical outcomes, polypharmacy presents a challenge in the treatment of RD (19). Considering that our study found that polypharmacy predicted medication non-adherence, the effects of polypharmacy on disease activity and clinical outcomes may be associated with poor treatment adherence.

In 1983, HADS was first introduced by Zigmond and Snaith (20) to assess anxiety and depression in the general patient population. The higher the HADS score, the more severe the symptoms of depression and anxiety can be considered (20). Since then, HADS has been used in various clinical situations. In our study, the HADS score was higher in patients with low treatment adherence than in those with high treatment adherence. In accordance with our study, Du et al. (21) showed that patients with systemic lupus erythematosus who were non-compliant with treatment had higher HADS scores than those who adhered to treatment. This could be due to depressive mood or anxiety triggering a reluctance to adhere to treatment. In this case, the importance of social support should be highlighted.

Study Limitations

The main limitations of this study are its cross-sectional, observational, and single-center design. Another limitation is that there may be biases due to patients' self-reported measures of adherence, such as the MMAS-8. Future studies with longitudinal designs and more diverse, multicentre samples may provide robust evidence for understanding this relationship.

Conclusion

This study provides valuable information on the diagnostic patterns, clinical and demographic characteristics, and medication adherence of elderly patients with RD. Medication adherence remains a critical factor in the effective management of RD, with demographic factors such as comorbidities and socioeconomic status playing influential roles. Future research should investigate the interactions between clinical, demographic, and behavioral factors and the factors that influence medication adherence in this patient group.

Ethics

Ethics Committee Approval: Before the study was conducted, ethics committee approval was obtained from Marmara University Faculty of Medicine Research Ethics Committee (approval number: 09.2019.1079, date: 06.12.2019).

Informed Consent: Informed consent was obtained from patients who agreed to participate in the study.

Footnotes

Authorship Contributions: Concept - N.Ö., M.T.D.; Design - N.Ö., M.T.D.; Data Collection or Processing - N.Ö., M.T.D.; Analysis or Interpretation - N.Ö., M.T.D.; Literature Search - N.Ö.; Writing - N.Ö., M.T.D.

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

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Can MPV be a Marker for Thyroid Malignancy in Thyroidectomy Patients?

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ABSTRACT

Introduction: Mean platelet volume (MPV) level can be affected by various factors. This study aimed to show the relationship between pre-operative MPV levels and histopathological diagnosis of thyroid malignancy in patients scheduled for surgery due to any thyroid-related disease.

Methods: A total of 263 patients who were diagnosed with thyroid-related disease in various clinics of Private Esencan Hospital, Clinic of General Surgery and decided to undergo thyroidectomy between January 2020-December 2023 were included in the study. Preoperative MPV values of the patients were studied in the biochemistry laboratory on ARCHITECT i1000SR and i2000SR (Abbott Diagnostics, Ireland) devices.

Results: The mean age of the patients was 53.4±18.4 (range: 18-83) years. The mean MPV value was 9.3±1.0 fL (range: 7.1-11.1). The presence of malignancy was detected in the histopathological examination of postoperative biopsies of a total of 111 (42.2%) patients. The mean MPV level in the group with malignancy was found to be significantly higher than in the group without malignancy (9.55 fL vs. 9.16 fL; p=0.001). Mean MPV levels were found to be similar among genders, operation types, presence of thyroiditis and presence of comorbid diseases (p>0.05 for each). In the logistic regression analysis, it was determined that MPV level was an independent risk factor for thyroid malignancy (p=0.001). Accordingly, it was determined that for each unit increase in MPV level, the odds ratio of having a thyroid malignancy in the patient was 1.6 times (1.2-2.1; risk coefficient) higher. In the receiver operating characteristic analysis, the sensitivity and specificity of the 9.45 fL threshold value for MPV in predicting thyroid malignancy were found to be 60.4% and 53.3%, respectively (area under the curve: 0.604; p=0.04; lower bound-upper bound: 0.536-0.672).

Conclusion: The findings obtained in this study, which compared only patients who were decided to have thyroidectomy, which is a rare situation in the literature, show that MPV levels before thyroidectomy in patients with thyroid cancer are significantly higher than in thyroidectomy patients without malignancy. MPV levels in patients who will undergo thyroidectomy can provide valuable information in predicting malignancy.

Keywords: Mean platelet volume, thyroidectomy, thyroid cancer, papillary thyroid cancer

Introduction

Thyroid cancers are tumors that arise from the cells of the thyroid gland. Thyroid cancers account for approximately 1% of all cancers, but are one of the most common endocrine cancers. It has been stated that the incidence of thyroid cancer is increasing worldwide. Among thyroid cancers, papillary, follicular, medullary, and anaplastic thyroid cancers are the most common. Fine needle aspiration biopsy is the gold standard method for diagnosis. The survival time is significantly longer in cases diagnosed early (1-3).

Mean platelet volume (MPV) is an important indicator of platelet functions. MPV is associated with platelet aggregation and activation. It has been shown that there is a relationship between MPV levels and various cancers, cardiovascular events, bleeding diseases, and many autoimmune disorders. For example, it has been reported that platelet volume increases in acute cardiac events, diabetes, and cancer cases. On the contrary, a decrease in MPV has been reported in cases of ulcerative colitis, some gastric tumors, and tuberculosis. MPV level has been shown to be an indicator of mortality and morbidity in many studies (4-7).

It has been shown that MPV level can be affected by thyroid hormone levels (8-11) and changes significantly in thyroid cancers (6,7,12-19). However, while many studies have reported an increase in MPV levels in thyroid cancer cases (6,7,12-17), some studies have reported no change (18,19), and some have even reported MPV decreases in these cases. This study aimed to show the relationship between pre-operative MPV levels and histopathological diagnosis of thyroid malignancy in patients scheduled for surgery due to any thyroid-related disease.

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Methods

A total of 263 patients who were diagnosed with thyroid-related disease in Private Esencan Hospital, Clinic of General Surgery and decided to undergo thyroidectomy between January 2020 and December 2023 were included in the study.

The study was conducted after obtaining approval from the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 104, date: 18.10.2024).

Preoperative MPV values of the patients were studied in the biochemistry laboratory on ARCHITECT i1000SR and i2000SR (Abbott Diagnostics, Ireland) devices. The process of collecting, transferring and testing samples was carried out in accordance with the recommendations of the manufacturers. Thyroid tissue material taken during the operation was examined histopathologically in the pathology laboratory.

Patients who were 18 years of age and above and who were scheduled to undergo thyroidectomy primarily due to thyroid disease were included in the study. Patients planned to undergo thyroidectomy due to non-thyroidal reasons, and patients under the age of 18 were excluded from the study.

Statistical Analysis

All statistical analyses in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as mean and standard deviation, and distributions of nominal or ordinal variables were given as numbers and percentages. Comparisons between groups in terms of categorical variables were made with the chi-square test. The Kolmogorov-Smirnov test was used to analyze whether continuous variables were normally distributed or not. Differences between groups for continuous variables were analyzed by Student's t-test, and comparisons of mean values between multiple groups were analyzed using analysis of variance. The risk coefficients of the variables in terms of thyroid malignancy were determined by logistic regression analysis. The predictive capacity of the 9.45 fL threshold value for MPV for malignancy was analyzed by receiver operating characteristic (ROC) analysis. The results were evaluated within the 95% confidence interval, and p-values <0.05 were considered significant.

Results

The mean age of the patients was 53.4±18.4 (range: 18-83) years. The mean MPV value was 9.3±1.0 fL (range: 7.1-11.1). The presence of malignancy was detected in the histopathological examination of postoperative biopsies of a total of 111 (42.2%) patients. There were signs of thyroiditis in 52 (19.8%) patients in the preoperative ultrasound examination. A total of 132 (50.2%) patients had comorbid diseases (Table 1).

The group with malignancy and the groups without malignancy were similar in terms of gender, presence of preoperative thyroiditis, presence of comorbid disease, distribution of the type of operation performed, and mean age (p>0.05; for each) (Table 1).

The mean MPV level in the group with malignancy was found to be significantly higher than in the group without malignancy (9.55 fL vs. 9.16 fL; p=0.001). Mean MPV levels were found to be similar between genders, operation types, presence of thyroiditis and presence of comorbid diseases (p>0.05; for each) (Table 2).

Table 1. Distributions according to some variables

	Total		No malignancy, (n=152)		Malignancy present, (n=111)		p
	n	%	n	%	n	%	
n	263	100	152	57.8	111	42.2	
Age (mean & SD) (years)	53.4	18.4	55.0	18.8	51.2	17.7	0.096
Gender							
Male	145	55.1	76	50.0	69	62.2	0.050
Female	118	44.9	76	50.0	42	37.8	
Operation type							
Bilateral total thyroidectomy	228	86.7	132	86.8	96	86.5	0.996
Unilateral total thyroidectomy	28	10.6	16	10.5	12	10.8	
Completion thyroidectomy	7	2.7	4	2.6	3	2.7	
Thyroiditis on preoperative USG							
Absent	211	80.2	123	80.9	88	79.3	0.741
Present	52	19.8	29	19.1	23	20.7	
Comorbid disease							
Absent	131	49.8	70	46.1	61	55.0	0.154
Present	132	50.2	82	53.9	50	45.0	

MPV: Mean plathelet volume, SD: Standard deviation, USG: Ultrasonography

Table 2. Comparison of mean MPV levels across different variables

	MPV (fL)		p
	Mean	SD	
Gender			
Male	9.42	0.94	0.071
Female	9.21	0.97	
Malignancy			
None	9.16	1.01	**0.001**
Present	9.55	0.083	
Operation type			
Bilateral total thyroidectomy	9.36	0.98	0.385
Unilateral total thyroidectomy	9.09	0.86	
Completion thyroidectomy	9.28	0.76	
Thyroiditis on preoperative USG			
Absent	9.31	0.98	0.482
Present	9.41	0.88	
Comorbid disease			
Absent	9.35	0.94	0.688
Present	9.30	0.98	

MPV: Mean plathelet volume, SD: Standard deviation, USG: Ultrasonography

In the logistic regression analysis, it was determined that MPV level was an independent risk factor for thyroid malignancy (p=0.001). Accordingly, it was determined that for each unit increase in MPV level, the probability of having a thyroid malignancy in the patient was 1.6 times (odds ratio: 1.2-2.1) higher. It was determined that sex, operation type, presence of thyroiditis on preoperative ultrasound, and comorbid disease were not independent risk factors for the presence of malignancy (p>0.05 for each) (Table 3).

In the ROC analysis, the sensitivity and specificity of the 9.45 fL threshold value for MPV in predicting thyroid malignancy were found to be 60.4% and 53.3%, respectively (area under the curve: 0.604; p=0.04; lower bound-upper bound: 0.536-0.672) (Figure 1).

Table 3. Logistic regression analyzes performed for the presence of thyroid malignancy

	p	Exp(B) (OR)	95% CI lower-upper
MPV	0.001	1.6	1.2-2.1
Gender			
Male			
Female	0.051	0.6	0.4-1.0
Operation type			
Bilateral total thyroidectomy			
Unilateral total thyroidectomy	0.939	1.0	0.5-2.3
Completion thyroidectomy	0.968	1.0	0.2-4.7
Thyroiditis			
Absent			
Present	0.741	1.1	0.6-2.0
Comorbid disease			
Absent			
Present	0.154	0.7	0.4-1.1

MPV: Mean plathelet volume, OR: Odds ratio, CI: Confidence interval

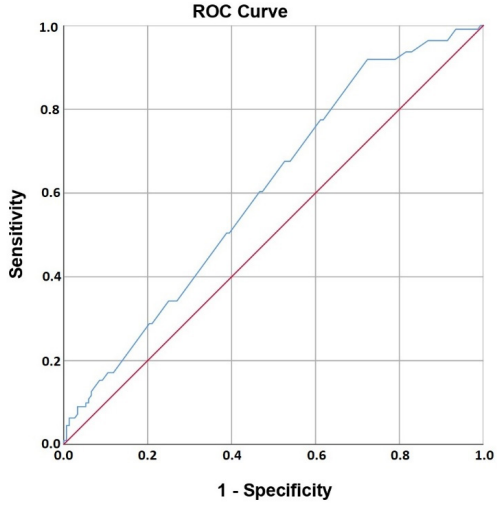

Figure 1. In the ROC analysis, the sensitivity and specificity of the 9.45 fL threshold value for MPV in predicting thyroid malignancy were found to be 60.4% and 53.3%, respectively (AUC: 0.604; p=0.04; LB-UB: 0.536-0.672) ROC: Receiver operating characteristic, MPV: Mean plathelet volume, AUC: Area under the curve, LB-UB: Lower bound-upper bound

Discussion

Platelet volume varies depending on platelet activation, platelet production, and the destruction resulting from many conditions in the body. Accordingly, it has been shown that measured MPV levels are affected by thyroid cancers (7,12-15). In this study, an increase in MPV levels was found in patients with thyroid malignancy.

Experimental and clinical evidence indicates that platelet activation during cancer contributes to the progression of the disease (19). Yu et al. (19) reported in their study that the mean MPV level was lower in thyroid cancer cases than in healthy controls, but they stated that the mechanism was not clear. Li et al. (20) showed that thyroid cancer recurrence was significantly increased in those with high MPV values. In the study by Dincel and Bayraktar (17), it was observed that the mean MPV value was significantly increased in papillary thyroid cancer cases compared to goiter or healthy controls (in the analysis performed by us). Baldane et al. (13) showed that the MPV levels were higher in patients with papillary carcinoma than in those with goiter and healthy controls, and that MPV levels decreased significantly after the operation. These researchers also found that the sensitivity and specificity of the threshold value of 7.8 fL for MPV in detecting thyroid cancer were 60% and 80%, respectively. In addition, some studies have reported that the average MPV level is significantly higher in thyroid cancer cases than in healthy controls (6,7,12,14-16). Healthy controls were not used in our study, instead, patients with thyroid disease and thyroidectomy decisions were included in the study. A comparison of MPV levels was conducted between patients with malignancy and a control group of patients. In our study, the mean MPV level in the group with malignancy was found to be significantly higher than the group without malignancy (9.55 fL vs. 9.16 fL). Additionally, logistic regression analysis revealed that MPV level was an independent risk factor for thyroid malignancy. Accordingly, it was determined that for each unit increase in MPV level, the probability of having a thyroid malignancy was 1.6 times higher. In addition to the ROC analysis, the sensitivity and specificity of the 9.45 fL threshold value for MPV in predicting thyroid malignancy were found to be 60.4% and 53.3%, respectively. All these findings show that platelet volume increases significantly in patients with thyroid malignancy and that the MPV level can provide important information in predicting the presence of malignancy in these cases. However, the fact that sensitivity and specificity values were not very high in the ROC analysis limits the use of MPV as a marker in these cases.

In our study, the average MPV levels were found to be similar between genders, operation types, presence of thyroiditis and presence of comorbid diseases, indicating that the MPV level was significantly affected only by the presence of malignancy among the variables in the study. In addition, the similarity of the groups in terms of other variables, which are not independent risk factors for malignancy, significantly increases the power of MPV in predicting malignancy.

Study Limitations

There were some limitations in our study. Since the study only aimed to determine the value of preoperative MPV in predicting thyroid malignancy, postoperative MPV levels were not examined. In addition, healthy controls were not included in the study because it was aimed to

determine whether there were differences in MPV levels among patients who were slated to undergo thyroidectomy.

Conclusion

The findings obtained in this study, which compared only patients who were decided for thyroidectomy, which is a rare situation in the literature, show that MPV levels before thyroidectomy in patients with thyroid cancer are significantly higher than in thyroidectomy patients without malignancy, and that MPV levels in patients who will undergo thyroidectomy can provide valuable information in predicting malignancy.

Ethics

Ethics Committee Approval: The study was conducted after obtaining approval from the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 104, date: 18.10.2024).

Informed Consent: Not applicable.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.Ö., M.M.S.; Concept - A.Ö., M.M.S.; Design - A.Ö., M.M.S.; Data Collection or Processing - A.Ö., M.M.S.; Analysis or Interpretation - A.Ö., M.M.S.; Literature Search - A.Ö., M.M.S.; Writing - A.Ö., M.M.S.

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The Experience of Pain Management for Pregnancy-Related Musculoskeletal Pain: A Retrospective Cohort Analysis

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ABSTRACT

Introduction: The primary aim of this study was to determine the ultrasound (US)-guided therapies for musculoskeletal pain during pregnancy. The secondary aim of the study was to define the parameters associated with treatment outcomes.

Methods: This retrospective cohort study included patients who had received US-guided injections for musculoskeletal pain during pregnancy and continued treatment for at least two months postpartum.

Results: Eighty patients, who underwent surgery at an average gestational age of 26.23±7.23 weeks, with an average age of 26.96±4.72 years and a body mass index of 27.11±3.39 kg/m^2 were included. Myofascial pain syndrome was the most commonly diagnosed condition. The three most common diagnoses were myofascial pain syndrome (20%), piriformis syndrome (18.8%) and plantar fasciitis (17.5%). The most commonly used treatments were trigger point injections (38, 47.5%) and piriformis injections (15, 18.8%). All patients experienced a decrease in their Numeric Rating Scale (NRS) from day 1 to day 30 ($p<0.001$). There is a moderate and significant positive correlation between the first measurement of NRS and weight gain during pregnancy ($r=0.242$, $p=0.031$).

Conclusion: US-guided pain interventions are safe and effective in all trimesters without maternal and neonatal complications. Pregnancy should not be considered a contraindication to interventional pain management, as these women can achieve significant relief of their symptoms.

Keywords: Pregnancy, musculoskeletal pain, ultrasound, injection, pain, NR

Introduction

Maternal health is an important public health issue worldwide. Interest in maternal morbidity, including musculoskeletal issues during pregnancy, is growing in recent literature, as the number of women with pregnancy-related problems and mortality rates in developing countries such as Türkiye is decreasing (1).

A wide range of musculoskeletal problems results from the biomechanical, hormonal and circulatory changes that occur during pregnancy. The cause may be an exacerbation of pre-existing symptoms or pregnancy-specific pain and/or inflammation. The center of gravity is affected by the position and weight of the expanding uterus, while hormonal fluctuations lead to ligament laxity and fluid retention. These changes increase the risk of musculoskeletal complaints, lower the threshold for developing spinal, hip, pelvic and wrist injuries, and lead to mechanical compression of structures such as the median nerve. Numerous studies have shown that almost all pregnant women experience musculoskeletal problems to varying degrees (2). Short-term disability symptoms occur in 25% of pregnant women (3). Spinal pain was reported most frequently. Other common problems were pain in the extremities, muscle cramps, hip pain, and heel pain (4).

Pain can have a negative impact on quality of life, the development of chronic pain syndrome, and the amount of time lost from work (5). More and more women are opting for elective cesarean sections or inductions to alleviate their discomfort. These complications and delivery options exacerbate maternal and fetal risk and incur significant costs (6,7). In addition, ambulatory challenges during acute pain episodes are suspected to be associated with life-threatening complications in pregnancy, including venous thromboembolism (7).

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The pregnant patients are usually undertreated because of fear of causing harm to the fetus. The medical treatment for musculoskeletal pain is unavailable. The main methods of pain relief during pregnancy are non-pharmacological and non-invasive (8). If conservative treatments prove inadequate, patients should receive interventional pain management. Due to the risk of radiation exposure to the mother and fetus, either computed tomography or scope-guided pain treatments are rarely suggested. Ultrasound (US) has become a well-known imaging modality for the diagnosis and treatment of musculoskeletal disorders during pregnancy (9). But still, there is fear of causing harm to both fetus and mother. Even if done, the effectiveness of US-guided injections in relieving pain during pregnancy is not well documented.

The primary aim of the study was to determine which interventions were used to treat musculoskeletal pain during pregnancy, using US to identify them. The secondary aim of the study was to determine effectiveness in relation to trimester, and other factors associated with treatment outcome.

Methods

Standard Protocol Approval and Patient Consent

In accordance with the Declaration of Helsinki, this retrospective cohort study was approved by the University of Health Sciences Türkiye, Van Training and Research Hospital Local Ethics Committee (approval number: 2023/20-03, date: 27.09.2023). Before participating in the study, all participants were required to give written and verbal informed consent. The manuscript was written in accordance with the STROBE (Strengthening Observational Study Reporting in Epidemiology) guideline. The study was conducted using a retrospective cohort approach. Primary and secondary outcomes were analyzed using medical records.

Study Design and Participants

This retrospective cohort analysis examined patients aged 18 years or older who received US-guided injections for the treatment of musculoskeletal pain during pregnancy and were monitored for at least two months after delivery. A search in the electronic database was performed between January 2021 and January 2023 with the diagnosis code pregnancy (Z33).

Patients without documentation or with insufficient follow-up were excluded. Patients who missed appointments or were unable to communicate were excluded from the study. Exclusion criteria included patients diagnosed with multiple musculoskeletal disorders, migraine, or nerve entrapment. Patients who presented with new neurological symptoms or abnormal, severe biochemical tests were excluded. Patients with coagulopathy, neuromuscular disease, rheumatologic disease, diabetes, hypertension, or high-risk conditions, including the risk of abortion or in vitro fertilization treatment, were excluded to avoid potential complications during invasive procedures.

The patients' medical records and follow-up data were reviewed retrospectively. Demographic and clinical characteristics of the participants such as age, body mass index (BMI), weight gain during pregnancy, parity, week of gestation when the intervention was performed, week of delivery, education level, occupation, exercise habits and weight of the infant were obtained from the medical records. Neck, back, lumbar spine, hip, knee, ankle, foot, hand, wrist, elbow, shoulder were identified as sites of musculoskeletal pain.

The diagnoses were categorized as follows: 1. Myofascial pain; 2. Piriformis syndrome; 3. Symptoms related to the mechanical sacroiliac joint; 4. Shoulder effusion (bursa or joint); 5. Plantar fasciitis; 6. Facet joint syndrome; 7. Medial/lateral epicondylitis; 8. Trochanteric bursitis; 9. Previous diagnosis of radiculopathy; 10. Dequervain's syndrome.

Initially, patients were advised to undergo conservative treatment, including physical rehabilitation, exercise, paracetamol, and topical non-steroidal anti-inflammatory drugs. For patients who did not respond to conservative treatment, intervention was suggested.

Intervention

In our pain medicine outpatient clinic, we performed the injections, without anesthesia, using an US machine equipped with a linear 13-5 MHz and convex C1-5-D probes (GE Healthcare, VolusonTM E6, Türkiye). The injections were administered as follows: 1. Trigger point injection; 2. Intrabursal/intraarticular injection; 3. Erector spinae plane block; 4. Medial facet branch injection; 5. Caudal epidural injection; 6. Piriformis injection; 7. Injection into the sacroiliac joint.

The trigger point injections and piriformis muscle injections were performed with US, and 3 cc of bupivacaine 0.25% (buvasin 0.5%) was administered. Trigger points were mostly on muscles around the neck and the scapula. Injections of 40 mg triamcinolone (kenacort) and 0.5% bupivacaine were administered under US guidance for intrabursal/intraarticular, sacroiliac joint, and fascial branch injections. Patients with radicular symptoms (previously diagnosed S1 radiculopathy) received a caudal epidural steroid injection of 8 mg dexamethasone under US-guidance. Each procedure was performed in accordance with a recommendation (9).

Outcome Measures and Follow-up

The primary aim of the study was to determine which US-guided therapies for musculoskeletal complaints were performed during pregnancy and to evaluate them in accordance with the medical data. The secondary aim of the study was to assess effectiveness according to trimester and other factors influencing treatment outcome. The Numeric Rating Scale 11 (NRS-11) was used to evaluate the effectiveness of the interventions before the procedure (NRS-1) and at one week (NRS-2) and one month (NRS-3) after the procedure. Patients were re-interviewed on the NRS (NRS-4) at least 30 days after their delivery. Medical records were used to assess the characteristics influencing the degree of pain before and after treatment.

Statistical Analysis

The descriptive statistics were presented in the following formats: frequency, percentage, mean, standard deviation, median, minimum, maximum, and 25^{th}-75^{th} percentiles (Q1-Q3), values. The Shapiro-Wilk test was employed to verify the normality assumption by analyzing the histogram, Q-Q plot, skewness, and kurtosis values. When analyzing the

difference between two groups' numerical data, the Mann-Whitney U test was employed when the data did not fit the normal distribution, and the Independent samples t-test was used when the data did. The Kruskal-Wallis H test was employed to analyze the difference between the numerical values of more than two groups when the data distribution did not conform to the normal distribution. The Bonferroni-Dunn Procedure was applied for pairwise comparisons in significant results. In the case of non-normally distributed data, the Friedman test was employed to determine whether the differences in time-dependent measurements varied between groups. When the numerical data did not follow a normal distribution, the relationships between them were assessed using the Spearman's correlation test. Statistical significance was determined by p-values that were less than 0.05. The SPSS 23.0 package was used for the analyses.

Results

Baseline Characteristics

After excluding 12 patients with missing data or different types of pain, the present study included 80 subjects, 68.8%, of whom were in the third trimester (Figure 1). The first visit to the pain clinic revealed a mean age of 26.96±4.72 years, a BMI of 27.11±3.39 kg/m^2, and a mean week of gestation of 26.23±7.23 weeks. The mean gestational week of delivery was 38.84±1.53 weeks. The average weight gain during pregnancy was 13.54±3.1 kilograms. The proportion of working patients was 46.3%. 48.8% of the participants had never exercised. Pregnancy complications included preterm delivery (10.0%), placental abnormality (5.0%), and pre-eclampsia (5.0%). An analysis of the categorical and numerical sociodemographic characteristics of the patients is presented in Tables 1, 2.

The characteristics of pain are summarized in Tables 1, 2. A mean NRS of 7.75±0.72 and a mean pain duration of 3.66±1.32 weeks were found. Most patients (56.2%) reported that their pain had started before pregnancy, and two-thirds of them reported that their pain had worsened during pregnancy. The pain occurred in the following regions: Back (18.8%), lower extremities (17.5%), heel (17.5%), hip (16.3%), upper extremities (11.3%), neck (7.5%), hand (7.5%) and shoulder (3.8%). The following diagnoses were made: myofascial pain syndrome (20%), piriformis syndrome (18.8%), plantar fasciitis (17.5%), lateral epicondylitis (10.0%), facet syndrome (10.0%), mechanical sacroiliac pain (6.3%), Dequervain's synovitis (5.0%), trochanteric bursitis (5.0%), S1 radiculopathy (3.8%), and subacromial effusion (3.8%). Trigger point injections were administered in 38 patients (37.5%), while 15 patients received piriformis injections. Intrabursal/intraarticular injections accounted for 8.8% of all injections. A total of six patients (7.5%) underwent caudal epidural injections for S1 radiculopathy, which was confirmed by magnetic resonance imaging. Six patients (7.5%), with back pain, underwent the erector spinae plane block. The sacroiliac joint was injected in five patients (6.3%). Injections of the medial branch of the facet were administered in three (3.8%) patients.

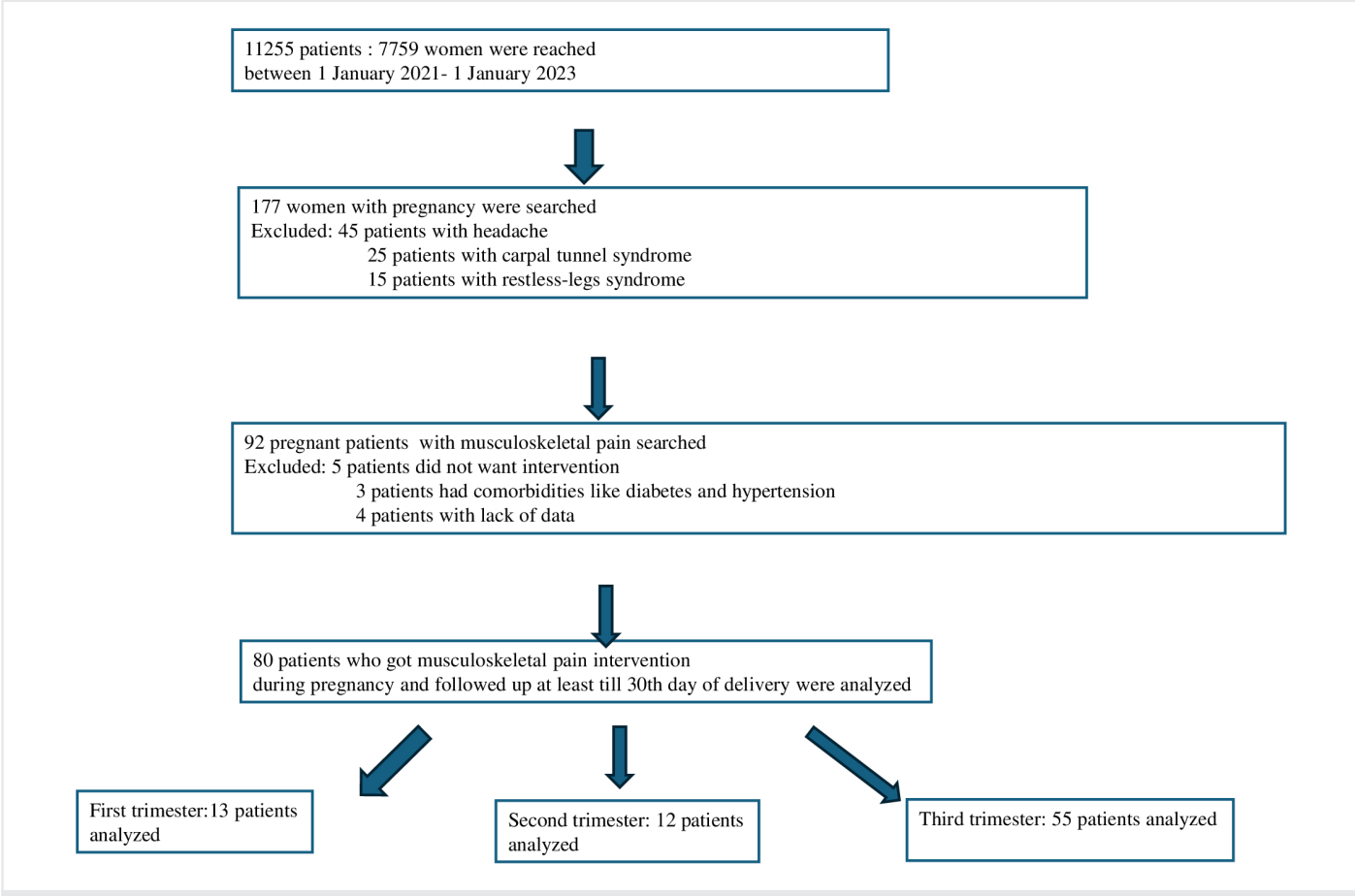

Figure 1. Flowchart diagram of the study

Table 1. Categorical variables of the patients

Variables	Categories	n	%
Patient trimester when admitted to pain department	1. Trimester	13	16.3%
	2. Trimester	12	15.0%
	3. Trimester	55	68.8%
Education level of patients	No education	5	6.3%
	Primary	27	33.8%
	High school	33	41.3%
	University	15	18.8%
Pain region	Neck	6	7.5%
	Back	15	18.8%
	Lower extremity	14	17.5%
	Upper extremity	9	11.3%
	Shoulder	3	3.8%
	Hand/fingers	6	7.5%
	Heel	14	17.5%
	Hip	13	16.3%
Diagnosis	Myofacial pain	16	20.0%
	Priformis syndrome	15	18.8%
	Mechanical sacroiliac pain	5	6.3%
	Subacromial effusion	3	3.8%
	Plantar fasiit	14	17.5%
	Facet syndrome	8	10.0%
	Sacral root radiculopathy	3	3.8%
	Medial/lateral epicodilitis	8	10.0%
	Trochanteric pain	4	5.0%
	Dequervain synovitis	4	5.0%
Has this pain begun during the pregnancy	Yes	35	43.8%
	No. the same as before pregnancy	15	18.8%
	Got worse after pregnancy	30	37.5%
Interventions	Trigger point injection	38	47.5%
	Joint injection	7	8.8%
	Erector spina plane block	6	7.5%
	Faset/medial branch injection	3	3.8%
	Caudal epidural injection	6	7.5%
	Priformis injection	15	18.8%
	Sacroiliac joint enj	5	6.3%
Pregnancy complication	Preterm birth	8	10.0%
	Plasenta anomaly	4	5.0%
	Preeclampsia	4	5.0%
	Other	0	0.0%
	None	64	80.0%
Sex of the infant	Male	31	38.8%
	Female	49	61.3%
How often do you exercise during pregnancy	Regular	8	10.0%
	Irregular	33	41.3%
	Never	39	48.8%
Do you employ during pregnancy?	Yes	37	46.3%
	No	43	53.8%

NRS Score Evaluation According to the Time and Three Trimesters

The correlation between specific numerical variables and time-dependent measurements of the NRS is examined in Table 3. According to this, there is a moderate and significant positive correlation between the first measurement of NRS and weight gain during pregnancy (r=0.242, p=0.031). The week of delivery and the NRS measurement in the first month show a weak and significant negative correlation (r=-0.247, p=0.027), while the duration of pain (weeks) shows a weak and significant inverse correlation (r=-0.238, p=0.034). There was a weak and statistically significant negative correlation between the postpartum NRS and the week of pregnancy in which the intervention was performed (r=-0.293, p=0.008).

The comparison of the time-dependent change in measurements for each group and the difference in NRS-1, NRS-2, NRS-3, and NRS-4 according to the specific categorical variables are shown in Table 4. Pregnant women who had new pain during pregnancy had a higher NRS-1 score than those who had pain before pregnancy (NRS-1: 8.06±0.73, p=0.006). The first week NRS measurement was significantly higher than NRS-2, NRS-3, and NRS-4 in all trimester groups (p=0.035).

In non-exercising individuals, each measurement in the test was different, evaluated at baseline NRS, first week NRS, first month NRS, and postpartum NRS (p<0.001). The first NRS was significantly higher than the second, third, and fourth NRS in the exercising group, and the third and fourth NRS in the exercising group were significantly higher than the second NRS (p<0.001). In contrast, there was no difference between the patients who exercised and those who did not.

In the first month, the NRS score of patients with pregnancy-related complications was significantly higher than that of patients with uncomplicated pregnancies (p=0.012).

Table 2. Numeric variables of the patients

Variables	n	Mean	SD	Median	Q1	Q3
Patient age	80	26.96	4.72	27	23	30.5
Pregnancy week when seen in the pain department	80	26.23	7.23	29	22.5	32
The delivery week	80	38.84	1.53	39	38	40
Patient height (cm)	80	164.23	7.61	163	158.5	170.5
Patient weight (kg)	80	73.2	10.81	71	67	79.5
Body mass index (kg/m^2)	80	27.11	3.39	26.57	24.62	28.83
Weight gain during pregnancy	80	13.54	3.15	12.5	11	16
Weight of the infant	58	3492.31	639.39	3715	3000	4000
Pain duration (weeks)	80	3.66	1.32	3.5	3	5
NRS initial	80	7.75	0.72	8	7	8
NRS after treatment in the first week	80	1.81	0.68	2	1	2
NRS 1 month after treatment	80	3.03	0.71	3	3	3
NRS postpartum 1. month	80	4.03	1.09	4	3	5

NRS: Numeric Rating Scale, SD: Standard deviation

Table 3. The correlation between numerical variables and NRS scores during time

		NRS initial (1)	NRS 1-week after the intervention (2)	NRS 1-month after the intervention (3)	NRS 1-month after the delivery (4)
NRS initial (1)	r		-0.126	0.168	-0.009
	p		0.265	0.135	0.934
NRS one week after the intervention (2)	r	-0.126		0.14	0.193
	p	0.265		0.216	0.086
NRS one month after the intervention (3)	r	0.168	0.14		-0.166
	p	0.135	0.216		0.142
NRS one month after the delivery (4)	r	-0.009	0.193	-0.166	
	p	0.934	0.086	0.142	
Patient age	r	-0.117	0.05	-0.115	0.155
	p	0.301	0.658	0.312	0.17
Pregnancy week when seen in the pain department	r	-0.023	-0.203	-0.193	**-0.293****
	p	0.84	0.071	0.086	**0.008**
The delivery week	r	-0.024	0.116	**-0.247***	0.1
	p	0.834	0.304	**0.027**	0.377
Weight gain during pregnancy	r	**0.242***	-0.007	0.093	-0.018
	p	**0.031**	0.947	0.409	0.871
Weight of the infant at delivery	r	-0.096	0.156	-0.184	0.172
	p	0.472	0.243	0.166	0.197
Pain duration (weeks)	r	0.031	-0.001	**-0.238***	-0.158
	p	0.787	0.991	**0.034**	0.162

Spearman correlation test, *p<0.05, **p<0.01, NRS: Numeric Rating Scale

Table 4. The change of NRS at time according to categorical variables

		NRS initial (1)		NRS one week after the intervention (2)		NRS one month after the intervention (3)		NRS one month after the delivery (4)		Dependent test (p)	Meaning
		Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p		
Total		7.75 (0.72)		1.81 (0.68)		3.03 (0.71)		4.03 (1.09)		**<0.001**[c]	**1>4>3>2**
Patient trimester when first admitted	1. Trimester	7.85 (0.8)	0.694[a]	2.23 (0.6)	**0.035**[a] **1>2** 1. trim > 2. trim	3.23 (0.44)	0.19[a]	4.23 (1.17)	0.24[a]	**<0.001**	**1>2, 3 4>2**
	2. Trimester	7.83 (0.83)		1.58 (0.67)		3.17 (0.72)		4.33 (1.07)		**<0.001**	**1>2, 3 4>2**
	3. Trimester	7.71 (0.69)		1.76 (0.67)		2.95 (0.76)		3.91 (1.08)		**<0.001**	**1>2, 3, 4 3, 4>2**
Has this pain begun during the pregnancy?	Yes (1)	8.06 (0.73)	**0.006**[a] Yes > no/ worse	1.69 (0.68)	0.114[a]	3.03 (0.82)	0.609[a]	3.86 (1.22)	0.209[a]	**<0.001**	**1>2, 3, 4 3, 4>2**
	No. the same as before pregnancy (2)	7.47 (0.64)		2.13 (0.74)		3.13 (0.52)		3.93 (1.16)		**<0.001**	**1>2, 3, 4 4>2, 3**
	Got worse after pregnancy (3)	7.53 (0.63)		1.8 (0.61)		2.97 (0.67)		4.27 (0.87)		**<0.001**	**1>2, 3, 4 -3, 4>2**
Pregnacy complication	No	7.72 (0.72)	0.485[b]	1.81 (0.66)	0.952[b]	2.91 (0.61)	0.012[b]	4.03 (1.05)	0.693[b]	**<0.001**	**1>4>3>2**
	Yes	7.87 (0.72)		1.81 (0.75)		3.5 (0.89)		4 (1.26)		**<0.001**	**1>2, 3, 4 -4>2**
Exercise	No	7.74 (0.64)	0.866[b]	1.74 (0.72)	0.327[b]	2.9 (0.68)	0.099[b]	4.21 (0.95)	0.099[b]	**<0.001**	**1>4>3>2**
	Regular-irregular	7.76 (0.8)		1.88 (0.64)		3.15 (0.73)		3.85 (1.2)		**<0.001**	**1>2, 3, 4 3, 4>2**
Do you employ during pregnancy?	Yes	7.76 (0.68)	0.845[b]	1.81 (0.7)	0.953[b]	3.11 (0.84)	0.546[b]	4.11 (0.99)	0.744[b]	**<0.001**	**1>2, 3, 4 3, 4>2**
	No	7.74 (0.76)		1.81 (0.66)		2.95 (0.58)		3.95 (1.17)		**<0.001**	**1>2, 3, 4 3, 4>2**

[a]Kruskal-Wallis H test with Bonferroni-Dunn Prosedure, [b]Mann-Whitney U test, [c]Friedman test with Bonferroni-Dunn Prosedure, NRS: Numeric Rating Scale, 1: NRS initial, 2: NRS one week after the intervention, 3: NRS one month after delivery, 4: NRS one month after delivery

During pregnancy, the first NRS was higher than the second, third, and fourth, with the third and fourth higher than the second in both employed and unemployed women. However, no difference was found between the NRS values of employed and unemployed women.

Discussion

This retrospective cohort study has drawn attention to the effectiveness of US-guided treatments for musculoskeletal pain during pregnancy. The highest frequency of pain interventions was during the third trimester. More intense pain correlated with weight gain during pregnancy. Treatment outcomes in the first month and in the postpartum period worsened with weight gain during pregnancy.

Most patients reported that their pain had occurred before pregnancy, and two-thirds of them reported that their pain had worsened during pregnancy. The most common areas of pain were the back and legs. Myofascial pain syndrome, piriformis syndrome, and plantar fasciitis were the most common diagnoses. Trigger point injections and piriformis injections were the most frequently performed US-guided procedures. From the first appointment to day 30, pain intensity decreased in all patients. The NRS score was consistently similar across the trimesters. Consequently, the therapies were beneficial in all three trimesters.

Patients treated in the first trimester had a higher initial NRS score than those treated in later trimesters. Patients who had no pain before pregnancy or who had gained weight during pregnancy had a higher initial NRS score. The effectiveness of the intervention during the first month was negatively correlated with the week of delivery and the duration of pain. In the postpartum period, pain intensity was inversely correlated with the week postpartum in which the intervention was performed, suggesting that effectiveness decreased as time after the intervention increased. In the first month, patients with pregnancy-related complications had a higher NRS score than patients with uncomplicated pregnancies. One month after the intervention, women who experienced pregnancy-related complications had a higher NRS score than women who did not.

During pregnancy, the cardiovascular, endocrine, renal, and musculoskeletal systems are significantly affected. Although the musculoskeletal system can be damaged at any time during pregnancy, the effects are most pronounced in the third trimester (4). As described in the literature, most of the women who participated in the study were in the third trimester of pregnancy. Increased musculoskeletal complaints in the third trimester of pregnancy have been associated with weight gain, fluid retention, and changes in posture and hormones (8,10,11). Weight gain in the present study also contributed to an increase in initial pain intensity. Treatment outcomes in the first month and in the postpartum period decreased with weight gain during pregnancy. This might be a result of higher initial pain, physical strain, or hormonal factors.

In the past, the need for antenatal exercise as a regular part of prenatal care was emphasized to reduce musculoskeletal discomfort and thus improve the overall health and well-being of pregnant women (12). In the current study, no difference in pain intensity was found between exercising and non-exercising women at any time point, but the intervention reduced pain intensity in both groups.

The interventions were done under US without any side effects or complications. This method was safe for both the mother and the fetus. Because of visualization of the anatomical structures around the injection site, the risk of injury to nerves, vessels, tendons, or any other structure is minimized. The US has no adverse effect on the fetus as previously shown (9).

Given that a biopsychosocial perspective can explain the experience of chronic pain, it is reasonable to assume that psychological factors, such as mental health diagnoses, may contribute to the severity of pain and impaired functioning in general and in those receiving treatment, as previously reported (13,14). In addition, treatment outcomes may be affected by the presence of anxiety and depression (13). However, due to the retrospective design, the current study did not examine the impact of mental illness on treatment outcomes.

Study Limitations

The current study has significant shortcomings, including a retrospective design, inadequate sample size, and lack of a control group. The impact these might have had on the interpretation of results is uncertain. Besides, the findings could have been influenced by other factors such as the placebo effect. The outcome of the treatment was assessed using the NRS. However, pain can also affect patients' overall quality of life, including their emotional state, mobility and sleep patterns. Therefore, no data are available on patient impairment or quality of life. Future research should use more validated methods to examine quality of life and impairment in a larger and more diverse sample of pregnant women, to verify and improve these findings.

Despite these limitations, the present study provides valuable insights into the treatment of musculoskeletal pain during pregnancy using US-guided injections. Fetal, maternal, and neonatal outcomes were monitored by perinatologists and pain physicians from the first appointment through the first month of delivery.

Conclusion

Pregnant women suffer from numerous pains and symptoms of the musculoskeletal system, especially in the third trimester, and often seek help. US-guided pain treatments are safe and effective in any trimester without causing problems for the mother or newborn. Interventional pain management should not be considered contraindicated in pregnancy, as pregnant women can experience significant relief of their symptoms, which impacts their quality of life in the prenatal period. Initial pain intensity was increased by the onset of pregnancy, increased weight gain and complications associated with pregnancy. Weight gain and a complicated pregnancy were associated with a poorer treatment outcome. However, there is still a need to conduct additional studies well-designed to identify predictors of more effective pain treatments during pregnancy. Randomized controlled trials exploring patient-reported outcomes, which could complement the clinical findings, are needed.

Ethics

Ethics Committee Approval: This retrospective cohort study was approved by the University of Health Sciences Türkiye, Van Training and Research Hospital Local Ethics Committee (approval number: 2023/20-03, date: 27.09.2023).

Informed Consent: Before participating in the study, all participants were required to give written and verbal informed consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.A.T., A.A.Y., Z.B., M.K.; Concept - S.A.T., H.T.; Design - S.A.T., A.A.Y., H.T.; Data Collection or Processing - S.A.T., A.A.Y., Z.B., M.K.; Analysis or Interpretation - S.A.T., Z.B.; Literature Search - S.A.T., A.A.Y., Z.B., M.K.; Writing - S.A.T., H.T.

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Follicular Lymphoma: Frequency and Timing of Treatment: Single Center Experience

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ABSTRACT

Introduction: This study aimed to investigate how often follicular lymphoma (FL) occurs in patients diagnosed with non-Hodgkin lymphoma (NHL). Additionally, we investigated whether patients with FL required treatment, and if so, whether the need for treatment arose at the initial diagnosis or during subsequent follow-up periods.

Methods: Six thousand five hundred sixty patients diagnosed with NHL or chronic lymphocytic leukemia were reached, and healthy data were obtained from 1,719 of them. Data from 176 patients diagnosed with FL were evaluated. Demographic information (age, gender) of the patients was collected. The classifications were grouped by taking into account World Health Organization data, the histological subtype of the tumor, gender and need for treatment were evaluated.

Results: Among the patients, 55.1% (n=97) were men and 44.9% (n=79) were women. The median age of those with FL was 50 years, with ages ranging from 18 to 87. When looking at histological subtypes, the FL accounts for 10.2% of cases (n=176). The proportion of patients requiring treatment was 70.9% (125), and the proportion of patients followed up without treatment was 27.8% (49). Of the patients who needed treatment, 57.1% (n=101) required it at the time of diagnosis and 13.6% (n=24) during follow-up.

Conclusion: FL, making up around 20% of all NHL, is the second most prevalent type of lymphoma in adults. The incidence, as well as the gender and age distribution, of FL can differ across populations. This may be related to ethnicity, geographical conditions, and socioeconomic status. In addition, the proportion of patients requiring treatment may also vary. When all these are taken into account, social differences are some of the main determinants in the approach to FL.

Keywords: Follicular lymphoma, frequency, treatment demand

Introduction

Non-Hodgkin's lymphoma (NHL) stands as the most common hematological malignancy worldwide, encompassing a diverse array of B-cell and T-cell proliferative disorders. Unlike Hodgkin's lymphoma, NHL is characterized by specific clinical features and the absence of Reed-Sternberg cells, as well as negative CD15 and CD30 staining in histological analyses. While there are over 40 major subtypes, the most prevalent forms include the indolent follicular lymphoma (FL) and the aggressive diffuse large B-cell lymphoma (DLBCL) (1). According to the latest World Health Organization (WHO) classification, DLBCL is the most frequent NHL in Western countries, accounting for about 31% of adult cases. Other common aggressive B-cell subtypes include mantle cell lymphoma (MCL) (6% of cases) and Burkitt lymphoma (BL) (2% of cases). Among indolent B-cell NHL, FL represents 22% of cases in Western nations, followed by marginal zone lymphoma (MZL) (8% of cases), chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL) (6% of cases), and lymphoplasmacytic lymphoma (LPL) (1% of cases). T-cell lymphomas, comprising only 10-15% of NHL diagnoses, primarily consist of peripheral T-cell lymphoma (6% of cases) and cutaneous T-cell lymphoma (4% of cases) (1).

Limited data exist for global comparisons, but a comprehensive international pathology study examining NHL subtype frequencies across 24 nations revealed that FL constituted a greater proportion in developed countries (25.5%) than in developing ones (15.3%) (2). While FL incidence rates plateaued in France during 2000-2009, they continued to rise in Australia from 1997-2008, Singapore from 1998-2012, and Japan from 1993-2008 (3-6).

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At initial diagnosis, FL is often found in an advanced stage, as demonstrated by bone marrow (BM) biopsy and positron emission tomography-based staging (7). However, approximately 10% to 15% of patients exhibit localized disease that may be treated with potentially curative radiotherapy. Another 20% to 25% of patients present with advanced stage, asymptomatic, and low-volume disease, which does not require immediate treatment; hence, observation is recommended for these cases until clear disease progression occurs. The remaining 60% to 70% of patients have advanced and/or high tumor burden disease that necessitates upfront systemic treatment (8).

Our research focused on determining how often this specific subtype occurred within the broader category of NHL. Additionally, we investigated whether patients with FL required treatment, and if so, whether the need for treatment arose at the initial diagnosis or during subsequent follow-up periods.

Methods

This study was designed retrospectively to evaluate the frequency of FL and the need for treatment. The study included data from patients with FL diagnosed at the University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Hematology between January 2008 and November 2024.

The study was conducted after obtaining approval from the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 127, date: 29.11.2024).

In total, 6,560 patients diagnosed with NHL or CLL were reached, and health data were obtained from 1,719 of them. Data from 176 patients diagnosed with FL were evaluated within this patient group.

Inclusion Criteria

- Patients with a diagnosis of FL confirmed histopathologically and immunohistochemically.

- Patients who were followed for at least 12 months after diagnosis.

- Patients with complete clinical and laboratory information in their electronic health record.

Exclusion Criteria

- Diagnosed with other hematological malignancies.

- Patients with insufficient clinical data records.

Demographic information (age, gender) of the patients was collected. The classifications were grouped by taking into account WHO data; the histological subtype of the tumor, gender and need for treatment were evaluated.

Statistical Analysis

The descriptive statistics of the qualitative variables in the study are presented as numbers and percentages, and the descriptive statistics of the quantitative variables are presented as mean, standard deviation, median, minimum, and maximum. The conformity of the quantitative variables to the normal distribution was evaluated with the Kolmogorov-Smirnov test.

Results

Among the patients, 55.1% (n=97) were men and 44.9% (n=79) were women. The median age of those with FL was 50 years, with ages ranging from 18 to 87. When looking at histological subtypes, aggressive B-cell subtypes include DLBCL, 35.6% of cases (n=612), T-cell lymphomas, 6.3% of cases (n=108), MCL, 4.8% of cases (n=82), BL, 2.3% of cases (n=39), and aggressive B-cell lymphoma, 2.2% of cases (n=38). Within indolent B-cell NHL, CLL/SLL, accounts for 25.6% of cases (n=440), FL accounts for 10.2% of cases (n=176), MZL accounts for 6.5% of cases (n=112), low grade B-cell lymphoma accounts for 3.8% of cases (n=64), hairy cell leukemia accounts for 2.3% of patients (n=39), and LPL accounts for 0.5% of cases (n=9). Histological subtypes of the cases are shown in Table 1.

The proportion of patients requiring treatment was 70.9% (125), and the proportion of patients followed up without treatment was 27.8% (n=49). Of the patients who needed treatment, 57.1% (n=101) needed treatment at the time of diagnosis and 13.6% (n=24) needed treatment during follow-up. Of the 24 patients treated during follow-up, 58.3% (n=14) were men and 41.7% (n=10) were women. Distributions according to treatment need are shown in Tables 2, 3.

Discussion

NHL is the leading type of blood cancer worldwide (9). It is more frequently seen in developed countries and includes more than 40

Table 1. Subtypes of non-Hodgkin's lymphoma

Diagnosis	(n=1719)	(%)
DLBCL	612	35.6
CLL/SLL	440	25.6
FL	176	10.2
MZL	112	6.5
NKTL	108	6.3
MCL	82	4.8
Low grade B-cell lymphoma	64	3.8
HCL	39	2.7
BL	39	2.7
High grade B-cell lymphoma	38	2.2
LPL	9	0.5

DLBCL: Diffuse large B-cell lymphoma, CLL: Chronic lymphocytic leukemia, SLL: Small lymphocytic lymphoma, FL: Follicular lymphoma, MZL: Marginal zone lymphoma, NK/TL: Natural killer/T-cell lymphoma, MCL: Mantle cell lymphoma, HCL: Hairy cell leukemia, BL: Burkitt lymphoma, LPL: Lymphoplasmacytic lymphoma

Table 2. Age, gender and treatment distribution

Follicular lymphoma	(n=176)
Gender	
Female	79 (44.9%)
Male	97 (55.1%)
Treatment	
At diagnosis	101 (57.3%)
No treatment	49 (27.8%)
During follow-up	24 (13.6%)
Unknown	2 (1.1%)
Age	50.5 (18-87)

Table 3. Need for treatment according to gender

Treatment	At diagnosis	Untreatment	During follow-up	Unknown
Females (n=79)	45	10	24	
Males (n=97)	56	14	25	2

distinct subtypes, each characterized by unique genetic, morphological, and clinical traits. The distribution of NHL subtypes varies according to age, gender, ethnicity, and geographic location (10).

In developed countries, FL comprises approximately 15-20% of adult NHL cases and is known for its slow-progressing nature (11). Our research, which included 1,719 NHL patients, found FL frequency to be 10.2%. This discrepancy may be attributed to differences in geography, race, socioeconomic conditions, and environmental factors.

In high-income countries, the age-standardized incidence rate of FL is about 2 to 3 per 100,000 person-years, with the median age at diagnosis falling in the 60s (12). Our study revealed a mean age of 50.

Unlike most NHL subtypes that show a higher male prevalence, FL exhibits a smaller or even reversed gender ratio, suggesting potential links to hormonal and reproductive factors. One analysis found an inverse relationship between FL risk and number of pregnancies, and a positive association with hormonal contraceptive use (13). In women, Sjögren's syndrome and smoking history were connected to an elevated risk of FL, whereas factors like alcohol consumption, hay fever, and food allergies were linked to a reduced likelihood of developing the disease. These findings indicate that FL has multiple contributing factors, with smoking potentially being a more significant risk factor for females (14). In our study, males comprised 55.1% of cases, while females accounted for 44.9%.

Various outcome measures have been developed for FL patients, including the FLIPI and tumor grade (15). The FLIPI evaluates five prognostic factors: age, stage, number of affected nodal regions, serum lactate dehydrogenase, and hemoglobin (16). An updated version, FLIPI-2, assesses five parameters, some of which overlap with the original FLIPI: beta-2 microglobulin, BM involvement, age, hemoglobin, and the longest diameter of the largest lymph node (17). The superiority of FLIPI-2 over the original FLIPI remains uncertain, with the latter still serving as a valuable prognostic tool (18). The FLIPI-2 is a simple and reliable prognostic tool that utilizes basic clinical information to assess outcomes in patients with FL. It plays a key role in improving prognostic predictions, guiding personalized treatment decisions, and organizing patient groups for prospective clinical studies. We analyzed cases using the FLIPI-2 score to determine treatment necessity.

FL treatment selection heavily depends on patient and disease characteristics. Most FL patients are diagnosed at an advanced stage. While many respond to initial treatment, they typically relapse and require additional therapy (19). Currently, conventional chemotherapy cannot cure advanced-stage FL. Consequently, asymptomatic patients may be observed without treatment (known as watchful waiting) for several years (20). In our study, 70.9% of patients required treatment, while 27.8% were monitored without intervention. Among those needing treatment, 57.1% required it at diagnosis, and 13.6% during follow-up.

Study Limitations

There were important limitations in our study. The limited number of patients was the most important limitation. Therefore, it was not possible to detail the subgroup analyses.

Conclusion

The frequency, gender and age distribution of FL may vary among societies. This may be related to ethnicity, geographical conditions and socioeconomic status. In addition, the proportion of patients requiring treatment may also vary. When all these are taken into account, social differences are one of the main determinants in the approach to FL.

Ethics

Ethics Committee Approval: The study was conducted after obtaining approval from the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 127, date: 29.11.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.K., İ.S.; Concept - A.K., M.H.D., R.E.; Design - A.K., İ.S., C.A., R.E.; Data Collection or Processing - V.C.Ç., İ.S., M.H.D., R.E.; Analysis or Interpretation - A.K., İ.S., C.A.; Literature Search - A.K., V.C.Ç., M.H.D., C.A.; Writing - A.K., R.E.

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More Aesthetic, Multi-Port Laparoscopic Appendectomy Using Conventional Instruments with Invisible Scar: A Case-Match Study

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ABSTRACT

Introduction: Laparoscopic appendectomy (LA) has become one of the most frequently performed abdominal surgeries worldwide, surpassing the traditional open technique. Over time, the increasing experience of surgeons in minimally invasive surgery and, notably because patients' aesthetic and cosmetological concerns have allowed surgeons to modify these techniques. In our study, we aimed to introduce the invisible scar laparoscopic appendectomy (ISLA) modified technique and present early postoperative outcomes.

Methods: Our study included 66 patients who underwent LA between August 2022 and April 2024. Half of these patients were in the ISLA group, and the other half were in the control group. The sequence of priority for matching the prognostic variables was age, sex, laparoscopic appendicitis grade, and body mass index. We retrospectively examined and compared the demographic data, discharge times, 30-day postoperative readmission rates, and operative data of these patients between the groups.

Results: There was no significant difference in postoperative 30-day complications, length of hospital stays, and drain usage between the two groups (p=0.708, p=0.841, and p=0.708, respectively). The duration of the operation was slightly longer in the ISLA group (p=0.006).

Conclusion: ISLA can be performed safely by experienced surgeons with appropriate case selection.

Keywords: Laparoscopy, appendectomy, invisible scar

Introduction

Since its inception, laparoscopic appendectomy (LA) has gained widespread adoption globally, surpassing the traditional open technique pioneered by McBurney (1,2). The advent of minimally invasive surgery and the growing expertise among surgeons have facilitated the increased application and technical refinement of LA over time. As a refinement of the standard 3-port access procedure, modifications have been made, including the reduction in the number of ports, variation in port entry sites, and downsizing of port dimensions (3-6).

Nowadays, increasing aesthetic concerns of patients have become a primary reason for these changes. Growing concerns about body image show that more and more patients want to remove scars from their navels for cosmetic reasons or due to belly piercings or tattoos (7). Some studies have shown that patients prefer scarless surgeries as long as the complication rates of the chosen surgical method are comparable to the current standard treatment (8,9). In fact, some studies indicate that people prefer scarless abdominal surgeries even if there is a slight increase in risk (10).

The aim of our study is to introduce the invisible scar laparoscopic appendectomy (ISLA) modified technique, utilizing standard laparoscopy instruments. In this technique, port entry locations have been adjusted to ensure that all incisions are situated below the bikini line. We also aim to present the early post-operative outcomes. In ISLA, all incisions are hidden by the suprapubic anatomical folds, which combines the advantages of multiport standard LA, with better cosmetic results. Additionally, there is the possibility of converting the procedure to traditional laparoscopic surgery at any time.

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Methods

The study commenced following approval from the University of Health Sciences Türkiye, Erzurum Faculty of Medicine Scientific Research Ethics Committee (approval number: 119, date: 10.07.2024). A total of 66 patients who underwent LA at the Clinic of General Surgery, Dr. Nevruz Erez State Hospital between August 2022 and April 2024 were retrospectively scanned and included. There were a total of 33 patients who underwent ISLA from the bikini line (group 1, n=33). As the control group, the same number of patients who underwent standard LA by the same surgeons in the same time period were of the same gender, similar age and body weight, and had laparoscopic grading system of acute appendicitis score ≤3A were selected (group 2, n=33) (11). The priority sequence of matching the prognostic variables was age, sex, laparoscopic appendicitis grade, and body mass index (BMI). Demographic data, BMI, American Society of Anesthesiologists (ASA) scores, discharge times, 30-day postoperative readmission status, and operative data were extracted from the hospital information management system and archive file records. In addition, patients were contacted via the phone numbers registered in the system and were asked whether they had applied to any external center regarding the surgery within the 30-day post-operative period, and this information was recorded. All patients were informed about this procedure before the operation and their informed consent was obtained.

Case Selection

In all cases, the diagnosis of acute appendicitis was confirmed preoperatively based on clinical presentation, laboratory values, and radiologic studies. Preoperative computed tomography (CT) scans were conducted for all patients. The surgeries were performed by two different surgeons employing identical methods (as described below). This approach was not favored by surgeons for selecting the surgical method for patients diagnosed with acute appendicitis during the specified time frame, particularly in cases where patients presented with maybe there was adhesions in the suprapubic region such as those with a history of cesarean section or existing surgical scars in visible abdominal areas. This method was not chosen in patients without aesthetic concerns and, due to there may be possible difficulties in the initial placement of the trocar, especially in obese patients with a BMI >30. Standard LA or conventional surgery was performed in cases of complicated acute appendicitis, which including perforation or intra-abdominal abscess evident on preoperative CT scans.

Operative Technique

Standard Laparoscopic Appendectomy

After induction of anesthesia, patients are placed in the supine position with the left arm positioned, prepared, and draped. After the necessary preparations are completed, a vertical 10 to 12 mm incision is made under the navel for the first trocar entry. Afterwards, pneumoperitoneum is provided by entering the abdomen with the Verres needle or Hasson technique, and a 10/12 mm trocar is inserted. A 10 mm 30-degree angled telescope is routinely used. After general intra-abdominal exploration, a 5 mm working trocar is inserted from the midline in the suprapubic region and another 10/12 mm working trocar from the lateral side of the left rectus muscle. LA is started on the left side in the Trendelenburg position (trocar entry locations are shown in Figure 1). After the mesoappendix dissection performed with laparoscopic energy devices, the appendix root is routinely closed with two non-absorbable polymer locking clips. Once the appendectomy is completed, the appendix is removed from the port in the umbilicus with the help of an endobag. The fascia of the umbilical trocar sites are routinely closed, and, if necessary, a drain is placed from the 5 mm trocar site. All patients in group 2 were operated on in this way.

Invisible Scar Laparoscopic Appendectomy

After induction of anesthesia, patients are placed in the supine position with the left arm closed, prepared and draped. After the necessary preparations are completed, the patient is placed in the Trendelenburg position to move the intra-abdominal organs away from the pelvis under the influence of gravity. This is done before the incision is made for the first trocar entry. Before the surgery, a transverse incision of 1.5 cm is made from the midline, approximately 2 cm above the symphysis pubis. This incision is below the line connecting the bilateral anterior superior iliac spine, marked at the level of the patient's daily underwear. The anterior abdominal fascia is passed through a vertical incision and the rectus muscles are reached. The rectus muscles are lateralized and the Retzius space is entered. In this interval, finger dissection is performed in the preperitoneal area to allow the peritoneum to be pulled out of the abdomen. The peritoneum is held with surgical instruments; the abdomen is entered with an open method, and the first 10/12 mm trocar is placed. Afterwards, a 10/12 mm trocar is inserted from the left inguinal region in the appropriate area according to the tracing of the inferior epigastric vessels by transillumination. In the continuation of the surgery, the camera is taken into the left 10/12 mm trocar, and another 5 mm trocar is inserted from the right inguinal region (Figure 2).

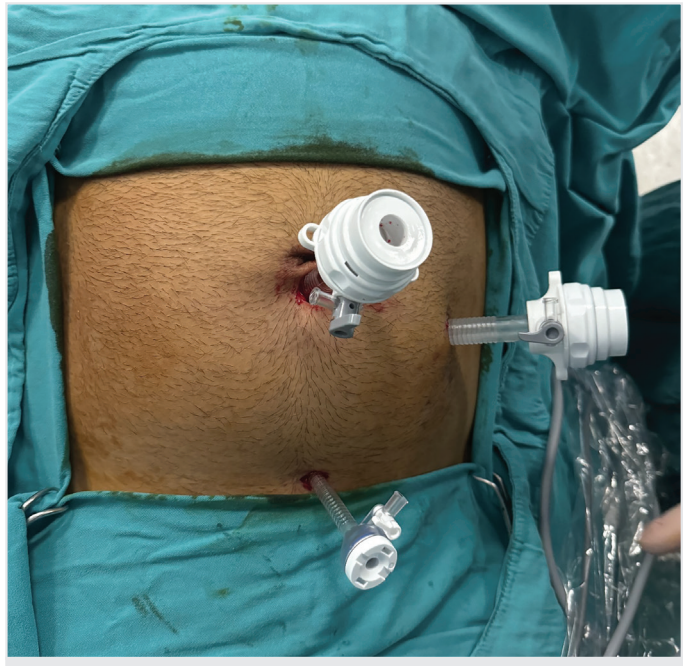

Figure 1. Standard LA port placement. Informed consent was obtained from the patient to use the image for scientific purposes

LA: Laparoscopic appendectomy

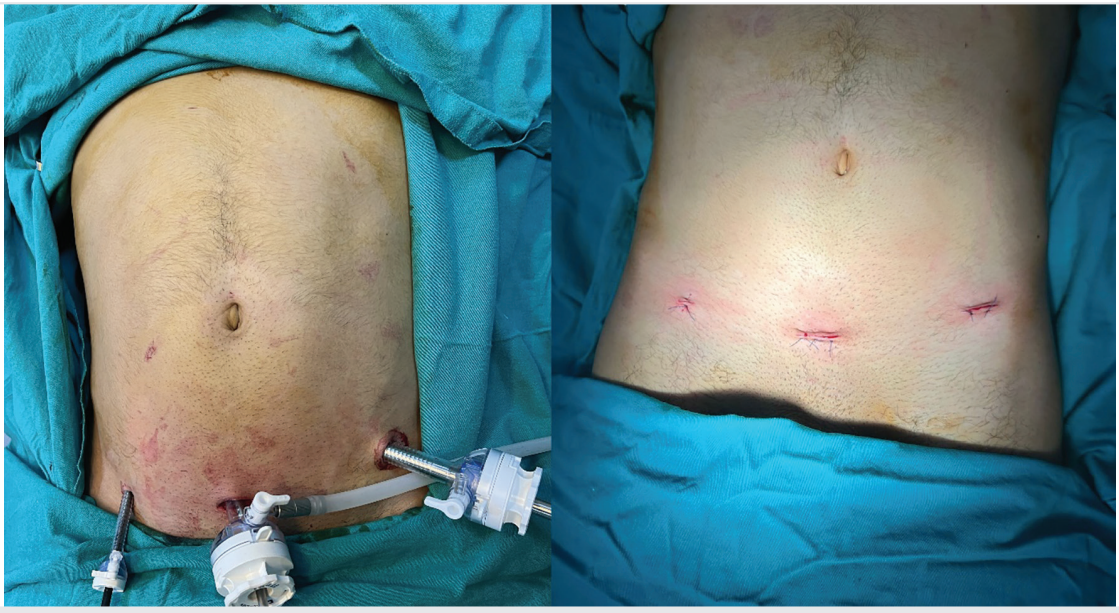

Figure 2. ISLA technique port placement and postoperative view. Informed consent was obtained from the patient to use the images for scientific purposes
ISLA: Invisible scar laparoscopic appendectomy

Afterwards, the patient is placed on the left side and the appendectomy is initiated. After mesoappendix dissection performed with laparoscopic energy devices, the appendix root is routinely closed with two non-absorbable polymer locking clips. Appendectomy is completed and then the appendix is removed from the port in the suprapubic region with the help of an endobag. The fascia of the suprapubic trocar sites is routinely closed and if necessary, a drain is placed from the 5 mm trocar site. All patients in group 1 were operated on in this way.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0. Descriptive statistics were presented as frequencies and percentages for categorical variables, and as means, standard deviations, medians, interquartile ranges, for numerical variables. The Student's t-test was applied for comparing numerical variables between two independent groups when the assumption of normal distribution was satisfied. In cases where normality was not assumed, the Mann-Whitney U test was utilized. The chi-square test was employed to examine group proportions. A p-value of less than 0.05 was considered indicative of statistical significance.

Results

A total of 66 patients were included in the study, with 33 patients in the ISLA group and 33 patients in the control group. All patients included in the study were classified as ASA I-II. Patients with a laparoscopic appendicitis grade of 3A or lower were included. The mean age of the patients was 24.29±5.81 years, and the mean BMI was 24.18±1.85 kg/m^2. The average duration of surgery was 48.80±13.30 minutes. The ISLA group and the standard LA group were similar in terms of age, gender, BMI, laparoscopic appendicitis grade, and ASA score (Table 1).

There was no significant difference in postoperative 30-day complications between the two groups (p=0.708). Complications were observed in a total of 8 patients across both groups. In the ISLA group, postoperative atelectasis developed in 1 patient, while superficial incisional surgical site infection developed in 2 patients. In the control group, postoperative subileus developed in 2 patients, superficial incisional surgical site infection in 2 patients, and atelectasis in 1 patient. These complications were classified as grade 1-2 according to the Clavien-Dindo classification.

The duration of the operation was longer in the ISLA group (p=0.006). There was no statistically significant difference in either hospital stay or drain usage (p=0.841 and p=0.708, respectively). The demographic and clinical characteristics of the ISLA and control groups are shown in Table 1.

Discussion

In recent times, there has been an extraordinary surge in interest in aesthetics and cosmetology, leading individuals to place greater emphasis on their appearance than ever before. Consequently, surgical scars have emerged as a significant concern. People resort to various measures such as anti-scar creams, tattoos for camouflage, and other methods to conceal surgical scars, underscoring the pressing need for innovative surgical techniques. All of these lead to the development of new surgical techniques and natural orifice transluminal endoscopic surgery procedures. These procedures, which are performed without any incision on the skin, are becoming more popular day by day (12). Our aim in this study is to present the ISLA method and its early results, which are similar to those of the standard method but in a more aesthetic way.

The benefits of standard LA over the open technique are mirrored in ISLA. These include the potential for extensive intra-abdominal exploration, reduced hospitalization duration, diminished postoperative pain and reduced narcotic usage, earlier resumption of normal activities, and decreased risk of wound infection (3,13). Our study found no significant disparities between groups regarding hospital stay, wound infection,

Table 1. Comparison of demographic and clinical characteristics between ISLA and control groups

		Group 1, ISLA (n=33)	Group 2, Control (n=33)	p
Age (median-IQR)		22.0-6	25.0-9	0.306
Sex	Female, n (%)	17 (51.5)	23 (69.7)	0.131
	Male n, (%)	16 (48.5)	10 (30.3)	
BMI (median-IQR)		24.0-2	24.0-3	0.112
ASA score	ASA I, n (%)	29 (87.9)	28 (84.8)	0.720
	ASA II, n (%)	4 (12.1)	5 (15.2)	
WBC (x10^6/L) (median-IQR)		13,000-3,000	14,000-4,000	0.820
CRP mg/L (median-IQR)		9.0-8	13.0-8	0.118
Length of hospital stay (hr) (median-IQR)		24-0	24.0-0	0.841
Complication	Yes, n (%)	3 (9.1)	5 (15.2)	0.708
	No, n (%)	30 (90.9)	28 (84.8)	
Operation time (min) (median-IQR)		50.0-18.0	40.0-5.0	**0.006**
Lap app grade	Grade 0, n (%)	1 (3.0)	1 (3.0)	0.650
	Grade 1, n (%)	6 (18.2)	5 (15.2)	
	Grade 2, n (%)	22 (66.7)	19 (57.6)	
	Grade 3A, n (%)	4 (12.1)	8 (24.2)	
Presence of drain	Yes, n (%)	3 (9.1)	5 (15.2)	0.708
	No, n (%)	30 (90.9)	28 (84.8)	

ISLA: Invisible scar laparoscopic appendectomy, IQR: Interquartile range, BMI: Body mass index, ASA: American Society of Anesthesiologists, WBC: White blood cell, CRP: C-reactive protein, hr.: Hour, min.: Minute

and other early postoperative complications. However, due to the lack of recorded discharge prescriptions, the impact of postoperative antibiotics on groups, particularly concerning complications like wound infection, remains unknown. The primary advantage of ISLA lies in its cosmetic appeal. Its superiority in aesthetics over standard or conventional open surgery is evident. By positioning all port entry sites beneath the patient's underwear, ISLA eliminates any visible scarring and allows patients to wear clothing of their choice. Furthermore, the incisions at the port entry points, aligned parallel to the skin's Langer's lines, promote optimal tissue healing.

The method by which the initial trocar entry should be made in laparoscopic surgery and which method is safer have been the subject of many studies. Ahmad et al. (14) reported in their meta-analysis that there is not enough evidence to support the use of one laparoscopic entry technique over another. The question of surgical safety always comes to mind in this technique. Contrary to popular belief, when appropriate patient selection occurs, the procedure is as safe as standard LA. The instruments used and the surgery performed are the same as the standard ones. In this technique, only the port entry locations are different. The most important point is that the first port is entered into the abdomen properly and safely (15). Since the method used by Ersoz et al. (16) for laparoscopic cholecystectomies is applied in appropriate cases in our clinic, our experience in entering the first port safely has increased over time. We recommend that the first port be entered via the open method from the suprapubic region, as described above. Although entering the first port from the lateral side may be easy in very thin patients, it may become difficult as BMI increases. We do not recommend routine Foley insertion before starting the surgery, but patients should ensure they urinate before being taken to the operating room. We do not find it safe to insert a Verres needle to achieve pneumoperitoneum from the first port entry site. Since we cannot sufficiently retract the abdominal wall in the suprapubic region from the intra-abdominal organs, we think that it may cause unwanted organ injuries, especially the bladder. In addition, accidental air insufflation into the preperitoneal area may make the continuation of the surgery very difficult. Entering the first port after reaching the abdomen with the Verres needle from the left upper quadrant, at the Palmer point, and providing pneumoperitoneum, is not a method we recommend. The lengthening of the peritoneum and preperitoneal area under the arcuate line while entering the trocar makes trocar insertion into the abdomen difficult. If this method is to be chosen, we recommend that the first port be entered with a video trocar. The first port entry may take more time and be more troublesome than standard LA. Once the first port is entered, the rest of the surgery is the same as standard LA, except for working in a slightly more uncomfortable position. After entering the ports, the camera is replaced with a 10/12 mm trocar on the left lateral side to increase the comfort of the surgeon.

Study Limitations

The biggest limitations of our study are: it is retrospective; the sample size is small; and patients are selected based on the method. The main reason for the small sample size is that ISLA was performed by only 2 surgeons who worked in our institution for a short time during the same period. In our study, the operation time was found to be longer in the ISLA group. This may be explained by the difficulty of the first trocar entry. The surgery times we calculate are based on the patients'

intubation and extubation times in the anesthesia form and may give misleading results. Although a difference of 10 minutes is statistically significant, we think this period is acceptable when applying an unconventional method in surgical practice and that the difference will decrease further as surgeons become more experienced. Likewise, not knowing the discharge prescriptions can be misleading regarding the development of postoperative wound infection. Prospective studies in larger patient groups are needed to prove the reliability of this method.

Conclusion

As a result, the prevalence of LA, its frequent performance in a young patient group, and the dramatic increase in aesthetic concerns among people, recently lead to an increase in the number of patients waiting for better cosmetic improvement, regardless of the surgical procedure performed. All these reasons lead surgeons to develop new methods that do not create additional costs, low complication rates, and a short learning curve. In this study, we propose modified LA as a new procedure, performed with standard laparoscopic instruments and resulting in invisible scars below the bikini line, that can be applied easily and safely, does not require additional costs, and has high patient satisfaction. We believe that in appropriate cases, in experienced hands, this method is as safe as standard LA, but more aesthetic. We recommend that surgeons carefully select the appropriate patient and apply this method only after gaining sufficient experience in using standard LA and laparoscopic instruments.

Ethics

Ethics Committee Approval: The study commenced following approval from the University of Health Sciences Türkiye, Erzurum Faculty of Medicine Scientific Research Ethics Committee (approval number: 119, date: 10.07.2024).

Informed Consent: All patients were informed about this procedure before the operation and their informed consent was obtained.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.D., H.Ş., M.G., E.K., Ö.A., M.Gül.; Concept - E.K., Ö.A., Design - E.K., Ö.A.; Data Collection or Processing - M.G., M.Gül.; Analysis or Interpretation - M.G., M.Gül.; Literature Search - A.D., H.Ş., M.G.; Writing - A.D., H.Ş., E.K.

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Predictors of Donor Site Morbidity Following Osteochondral Graft Harvesting from the Healthy Knee using Lysholm Knee Score

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ABSTRACT

Introduction: Donor site morbidity (DSM) is a notable complication following osteochondral graft harvesting for mosaicplasty, impacting patient outcomes despite the procedure's efficacy in treating cartilage defects. Identifying predictors of DSM is essential for optimizing patient selection and surgical techniques. To determine the incidence and predictors of DSM in patients undergoing osteochondral graft harvesting from the knee, focusing on factors such as age, gender, body mass index (BMI), donor site location, graft size, and number of grafts.

Methods: A retrospective review was conducted on 52 patients (57 knees) who underwent osteochondral graft harvesting for talus osteochondral lesions between 2015 and 2024. The Lysholm knee score (LKS) was used to evaluate DSM, with scores categorized as excellent (>90), good (84-90), fair (65-83), or poor (<65). Clinical and demographic data were analyzed to identify predictors of DSM.

Results: The mean follow-up was 36.2±26.6 months. The mean LKS improved significantly over time, reaching 97.1±4.1 after 12 months. DSM, defined as an LKS below "excellent," was observed in 9.8% of knees. No significant associations were found between DSM and predictors such as age, gender, BMI, donor site location, or the number and size of grafts harvested. Complications were minimal, with only one postoperative hemarthrosis and two cases of anterior knee pain with deep knee flexion.

Conclusion: DSM following osteochondral graft harvesting is relatively low, with most patients achieving excellent outcomes. No clinical or demographic predictors were significantly associated with DSM, suggesting that careful surgical technique may mitigate potential morbidity.

Keywords: Osteochondral graft harvesting, donor site morbidity, mosaicplasty, knee pain, osteoarthritis, predictors

Introduction

Autologous osteochondral grafting, also called mosaicplasty, is a common treatment for large and deep cartilage lesions in load-bearing joints, such as the knee and ankle. Initially described by Hangody et al. (1), this technique has become widely accepted for treating focal full-thickness chondral lesions of the knee. It involves harvesting one or more cylindrical autologous osteochondral plugs from the non-weight-bearing areas of the femoral condyle and transplanting them into matching sockets at the defect site (1). This method offers significant advantages, including delivering native cartilage and addressing subchondral defects in a single procedure. Additionally, it is cost-effective and allows for a shorter rehabilitation period (2). While it has demonstrated favorable outcomes in restoring joint function and reducing pain at the site of the lesion, concerns about donor site morbidity (DSM) persist. DSM refers to the complications that arise at the site where the graft is harvested, including pain, functional impairment, and the development of osteoarthritis. The incidence of DSM varies widely across studies from 6% to 20%, with reports ranging from negligible to significant morbidity rates (3-5). This variability underscores the need for a more nuanced understanding of the factors contributing to DSM.

Despite the widespread use of osteochondral grafting, there remains a lack of consensus on the predictors of DSM. Existing literature has provided conflicting results regarding the impact of factors such as patient age, body mass index (BMI), gender, the number of grafts harvested, and the size of the grafts, on the likelihood and severity of DSM (3-8). Moreover, while some studies have suggested that increased age and higher BMI are associated with poorer outcomes, others have found no significant correlation (9). Additionally, the influence of gender on DSM is not well understood, with some evidence indicating potential differences in outcomes between male and female patients (4,5,10).

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These inconsistencies highlight a critical gap in the research that needs to be addressed to optimize patient selection and surgical techniques, thereby minimizing the risk of DSM.

This study hypothesizes that the incidence of DSM following osteochondral graft harvesting is significantly influenced by patient-specific factors such as age, BMI, and sex, as well as procedural factors, including the number and size of the grafts harvested. Specifically, it is hypothesized that older age, higher BMI, and harvesting multiple or larger grafts are associated with increased DSM. The study also posits that gender may play a role in the incidence and severity of DSM, with potential differences in outcomes between male and female patients. By identifying these predictors, the study aims to contribute to a more individualized approach to osteochondral grafting, ultimately improving patient outcomes.

Methods

Patients and Study Design

This retrospective study was conducted on a cohort of patients who underwent osteochondral graft harvesting as part of surgical treatment for talus osteochondral lesions between 2015 and 2024 at the authors' institution. The inclusion criteria were: 1) Patients who had undergone osteochondral graft harvesting from the knee using the mosaicplasty technique, 2) patients with complete clinical and radiological data available for analysis. Patients with prior knee surgeries, pre-existing knee conditions, or incomplete follow-up data were excluded from the study. During the study period, 76 patients were treated for talus osteochondral lesions. Of these, 21 patients were excluded because they received acellular cartilage scaffolds rather than osteochondral grafts from the knee. From the remaining 55 patients, one patient was excluded because of death, and two patients were lost to follow-up. Consequently, 52 patients were included in the study. Since five patients underwent bilateral ankle procedures, a total of 57 knees were analyzed for comparison. The University of Health Sciences Türkiye, İstanbul Training and Research Hospital Institutional Review Board approved the study (approval number: 105, date: 08.11.2024), and informed consent was obtained from all participants. All study procedures were conducted following the ethical guidelines outlined in the Declaration of Helsinki and its subsequent amendments.

Surgical Technique and Postoperative Rehabilitation

All patients underwent osteochondral graft harvesting utilizing the Mosaicplasty technique. The procedure was conducted with the patient in a supine position under spinal anesthesia. A lateral parapatellar arthrotomy was performed to gain access to the femoral condyle. Cylindrical osteochondral grafts were harvested from the non-weight-bearing regions of the lateral femoral condyle using a dedicated harvesting instrument. The diameter of the grafts ranged from 6 mm to 10 mm, depending on the dimensions of the defect being treated (Figure 1). When multiple grafts were required, meticulous care was taken to minimize the cumulative donor site defect size. Following the harvesting procedure, the donor site defects were either allowed to heal by secondary intention or filled with a synthetic collagen membrane.

A below-knee splint was applied postoperatively due to the medial malleolar osteotomy performed in all patients. Patients were instructed to limit weight-bearing on the operated leg for four weeks and to follow a structured rehabilitation program. Cryotherapy was applied around the knee, and an elastic bandage was used for compression. Full-range active knee range-of-motion (ROM) exercises were initiated on the first postoperative day.

Outcome Measurements

In this study, the primary outcome measure was the Lysholm knee score (LKS) (11). LKS is a patient-reported score from 0 to 100, which evaluates limping, using crutches or canes, locking sensation and instability of the knee, pain, swelling, stair climbing, and squatting. The scores were classified as excellent (>90), good (84-90), fair (65-83), and poor (<65) (12). DSM was defined as an LKS not categorized as "excellent". The patient's knee ROM, patellar grind test results, and functional movements were evaluated at the final follow-up. All complications observed during the follow-up period were recorded, including early postoperative hemarthrosis, superficial or deep infections at the donor site, and any secondary procedures. Radiological assessments were conducted using standard anteroposterior and lateral radiographs to detect osteoarthritic changes at the donor site. The Kellgren-Lawrence grading system was employed for the classification of the severity of these changes. In addition, imaging evaluations, such as magnetic resonance imaging (MRI), were reviewed when applicable.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics Base v23 (IBM Corp., Armonk, NY). Descriptive statistics were presented as mean

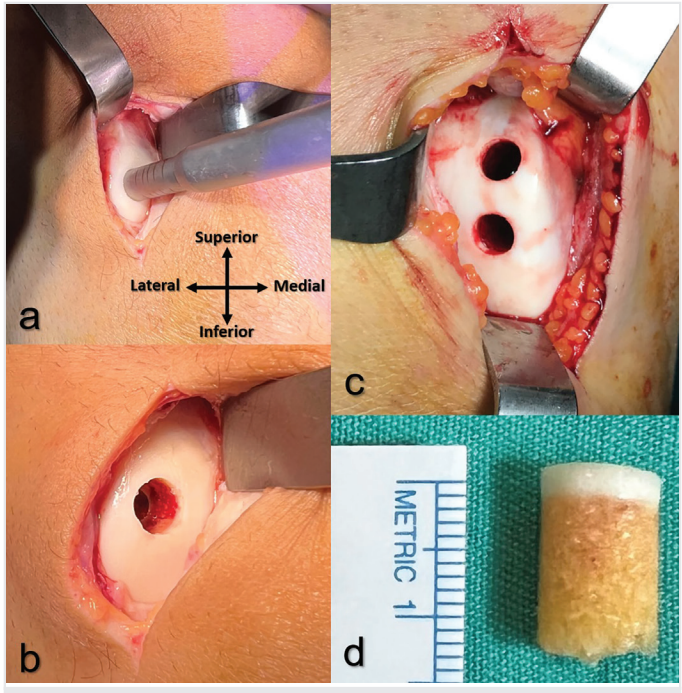

Figure 1. Osteochondral graft harvesting using the mosaicplasty technique. (a) Exposure of the femoral condyle through lateral parapatellar arthrotomy. (b) Single cylindrical graft harvest site. (c) Two cylindrical graft harvest sites. (d) An 8 mm cylindrical osteochondral graft specimen. Informed consent was obtained from the patient to use the images for scientific purposes

± standard deviation for continuous variables and as frequencies and percentages for categorical data. The normality of continuous variables, including LKS, was assessed using the Shapiro-Wilk test, Kolmogorov-Smirnov test, and visual inspection. Differences in LKS scores between groups (e.g., gender and defect filling) were evaluated using the independent samples t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. For patients with multiple LKS measurements, the Wilcoxon signed-rank test analyzed changes between the first and second assessments. The relationship between the LKS and clinical and demographic variables was evaluated using Pearson's correlation test. A linear regression analysis was performed to identify predictors of the final LKS. Variance Inflation Factor (VIF) was used to check for multicollinearity, and predictors with VIF >10 were excluded. Results were considered statistically significant at $p<0.05$.

Results

The study included 52 patients (57 knees), with a mean age of 42.8±12.7 years (range: 17-68). The cohort consisted of 23 males and 29 females. The mean follow-up period was 36.2±26.6 months (range: 1-108). Demographic and clinical characteristics of the study population are presented in Table 1.

Lysholm Knee Score Over Time

Seventy assessment points were analyzed, including repeated LKS measurements from 13 patients. A significant positive correlation was found between the LKS and time, indicating an improvement in scores over time ($r=0.398$, $p=0.001$). In the first three months, the mean LKS was 74.6 (range: 38-95). In the second quarter, the mean LKS increased to 81.1 (range: 54-94). Between 6 and 12 months, the mean LKS further improved to 87.8 (scores: 71-100). After 12 months, the mean LKS reached 97.1 (range: 80-100) (Figure 2). In the 13 patients with repeated measurements, there was an interval of 10 months between the first and second assessments. The mean LKS significantly increased from 79.9 to 94.2 (Table 2).

Predictors of Donor Site Morbidity following Osteochondral Harvesting

In this analysis, patients with a follow-up period of less than 12 months were excluded due to significant improvements observed in patients followed for more than 12 months. For the 51 knees with a follow-up exceeding 12 months, the mean LKS was 97.0±4.1 (range: 80-100). Of these, 5 knees (9.8%) had LKS categorized as good, while 46 (90.2%) were classified as excellent. No significant correlation was found between

Table 1. Demographic and clinical characteristics of patients

Variables	Data
Number of patients	52
Number of knees	57
Age at the time of operation (years ± SD, range)	42.8±12.7 (17-68)
Gender (M/F)	23/29
Side (R/L)	22/35
Height (cm ± SD, range)	165.4±8.2 (146-184)
Weight (kg ± SD, range)	77.3±11.5 (52-105)
BMI (kg/m^2 ± SD, range)	28.3±4.3 (19-39)
Number of osteochondral grafts (mean ± SD, range)	1.7±0.6 (1-3)
Graft area (mm^2 ± SD, range)	70.5±27.6 (28-150)
Follow-up (months ± SD, range)	36.2±26.6 (1-108)

SD: Standard deviation, M: Male, F: Female, R: Right, L: Left, BMI: Body mass index

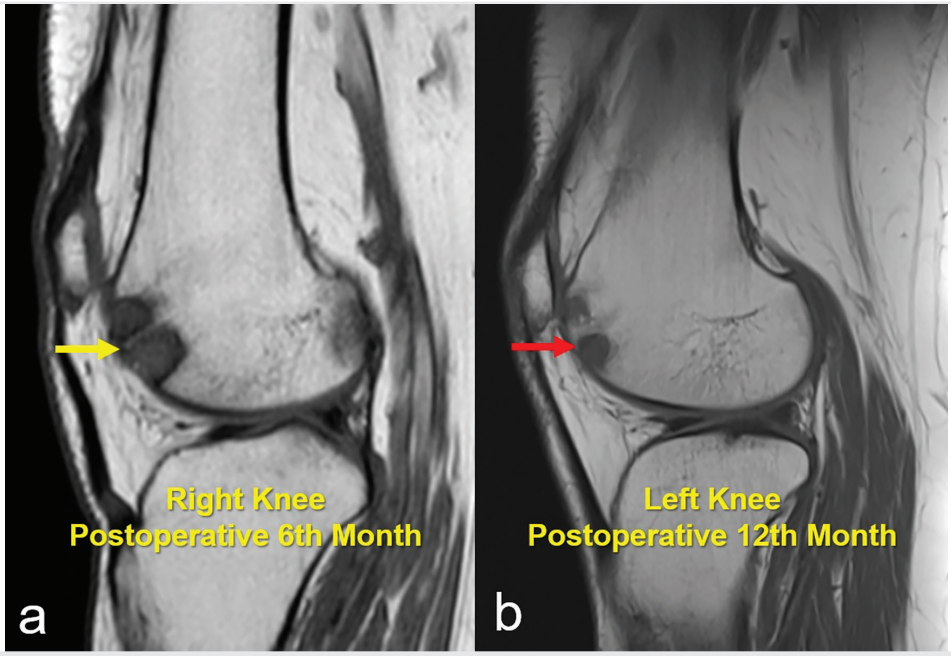

Figure 2. LKS over time. (a) Scatter plot showing LKS by follow-up period (months), with a trend line indicating a positive correlation over time ($r=0.398$, $p=0.001$). (b) Box plot displaying LKS grouped by follow-up periods: 0-3 months (mean: 74.6), 3-6 months (mean: 81.1), 6-12 months (mean: 87.8), and 12+ months (mean: 97.1). The scores improve progressively with longer follow-up periods

LKS: Lysholm knee score

final LKS values and clinical or demographic characteristics (Table 3). At the final follow-up, LKS scores were similar between males and females (97.4±4.7 vs. 96.7±3.7, p=0.562). Additionally, there was no significant difference in LKS scores between patients who received a collagen matrix at the donor site (n=10, 96.4±3.4) and those who did not (n=41, 97.1±4.3, p=0.568).

A linear regression analysis was conducted to explore the relationship between LKS and demographic and clinical variables. Due to a high correlation between height, weight, and BMI, there was significant multicollinearity (VIF >10), height and weight were excluded, and only BMI was included in the analysis. The model included the following predictors: age, gender, BMI, follow-up duration, donor area, number of grafts, and defect filling. None of these predictors demonstrated a statistically significant association with the final LKS (Table 4). The overall model had low explanatory power (R^2=0.103, adjusted R^2=-0.043).

Imaging Findings

No evidence of osteoarthritic changes was identified in any of the patients through radiographic examination of the knee. In a patient who received grafts from both knees six months apart, an MRI was performed one year after the initial operation, due to a catching sensation in the knee. The MRI results demonstrated that the donor area exhibited a significantly greater degree of filling in the knee at the one-year follow-up compared to the knee at the six-month follow-up (Figure 3).

Complications

One patient developed postoperative hemarthrosis, which required hematoma aspiration on the first postoperative day. The patient's symptoms resolved after applying cryotherapy and a compression bandage, and no recurrence occurred. No deep or superficial infections were observed in any patient. Two patients reported anterior knee pain at the end range of deep flexion. Additionally, two patients experienced occasional knee catching; however, their patellar mobility was normal on examination, and grind tests were negative. Apart from these issues, no other complications were observed in this series.

Table 2. Change in the consecutive assessment of LKS in 13 patients with multiple assessments

Variables	First time	Second time	p
Follow-up time	5.2 (1-11)	15.2 (11-21)	
LKS	79.9±17.3	94.2±1.5	**0.005***

*The Wilcoxon signed-rank test, LKS: Lysholm knee score

Discussion

The results of this study indicate that DSM following osteochondral graft harvesting from the knee is relatively low, with only 9.8% of knees exhibiting LKS below the "excellent" category after one year. Most of the patients demonstrated significant improvements in LKS over time, ultimately achieving optimal knee function with minimal complications. Patients can be reassured that donor site symptoms typically diminish and resolve completely by the end of the first year. We hypothesized that DSM might be associated with factors such as age, gender, BMI, graft area, number of grafts harvested, and the use of collagen matrix to fill the donor site. However, our findings did not support these hypotheses. No significant differences in knee function were observed between male and female patients. Similarly, although we anticipated that harvesting a larger number of grafts or larger graft size might lead to poorer outcomes, no correlation was found between LKS and either graft area or the number of grafts harvested. In our study, 91.2% of cases involved harvesting only one or two grafts, representing a relatively small donor site area that did not significantly impact knee function. We also speculated that older age might delay donor site healing, potentially resulting in functional impairment or osteoarthritic changes. Nevertheless, no relationship was found between age and knee function outcomes. Notably, our study encompassed a wide age range, from 17 to 68 years. Finally, while filling the donor site with a collagen membrane was hypothesized to accelerate healing and improve cartilage quality, this intervention did not show a measurable effect on functional outcomes. Overall, the low morbidity rate and minimal impact on knee function suggest that autologous osteochondral graft harvesting is a safe procedure. The results appear to be unaffected by demographic

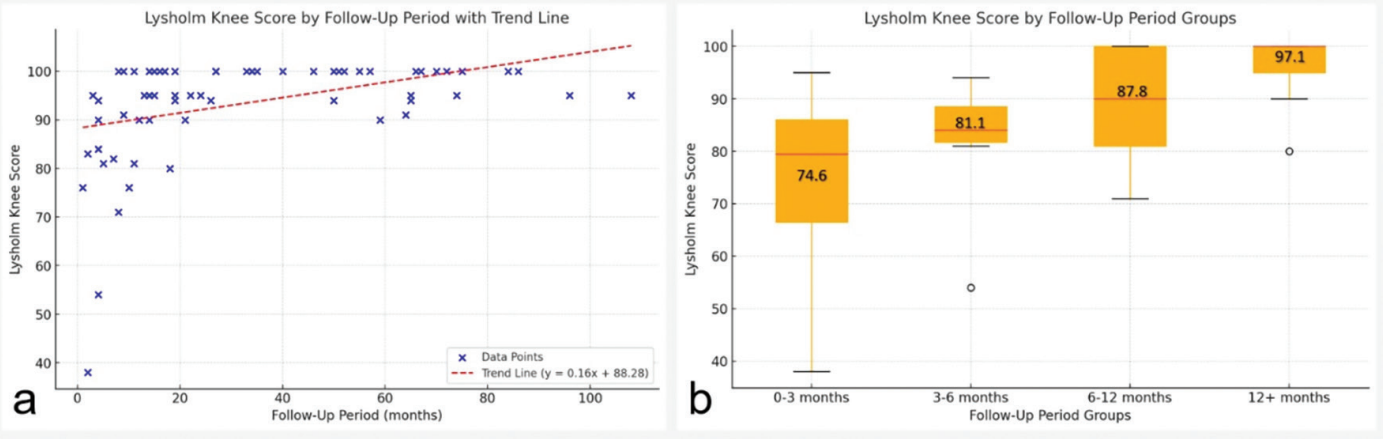

Figure 3. MRI Comparison of donor site healing in bilateral knees (a) Right knee at the 6-month postoperative follow-up (yellow arrow) showing incomplete donor site filling. (b) The left knee at the 12-month postoperative follow-up (red arrow) demonstrated significantly greater donor site filling. The MRI highlights improved donor site healing with a longer follow-up duration

MRI: Magnetic resonance imaging

or clinical characteristics, reinforcing the reliability and efficacy of this technique.

In the literature, limited studies specifically focus on DSM following osteochondral graft harvesting from a healthy knee (Table 5) (7,9,10,13-19). These studies use various parameters to assess knee function and outcome measurements, leading to conflicting and inconsistent results. We believe that the differences in the definition of DSM, the follow-up duration, and the relatively small sample sizes in some studies may account for these discrepancies in outcomes.

The length of follow-up has a significant impact on the reported outcomes of DSM. In our study, DSM symptoms typically resolved within the first year, with most patients achieving excellent LKS. This is consistent with Iwasaki et al. (13), who reported complete resolution of donor site symptoms by 26 months postoperatively. In contrast, Reddy et al. (14) observed persistent knee instability in some patients at a mean follow-up of 47 months. Andrade et al. (4) highlighted that DSM rates varied according to the length of follow-up, with knee-to-knee mosaicplasty procedures reporting morbidity rates ranging from 5.9% to 22%. Our results suggest that shorter follow-ups may underestimate DSM, while longer follow-ups, such as those reported by Paul et al. (10), highlight gradual improvement over time.

In the current study, no significant relationship was found between age and knee function outcomes. This is consistent with the findings of Paul et al. (10) and Nakagawa et al. (9), who reported no significant effect of age on DSM. However, Kurtuluş et al. (19) found that older patients had lower LKS and more degenerative changes. Similarly, Matricali et al. (3) suggested that age may influence the healing potential of donor sites, with older patients at higher risk of osteoarthritic changes. The wide age range of our study (17 to 68 years) supports the conclusion that DSM is generally low regardless of age, although older patients may require closer follow-up for degenerative changes.

The results of our study demonstrated no statistically significant differences in knee function outcomes between male and female patients. Both groups exhibited comparable LKS and overall recovery profiles. This finding is consistent with Guo et al. (18), who reported no correlation between gender and functional outcomes, including LKS and MRI findings, after osteochondral graft harvesting. Similarly, Andrade et al. (4) concluded that gender did not significantly influence DSM following mosaicplasty, emphasizing that other factors, such as graft size and location, were more influential. In contrast, Kurtuluş et al. (19) observed lower visual analog scale pain scores in female patients, which suggests the potential for differences in pain perception or reporting between genders. Moreover, Bexkens et al. (5) documented a DSM rate of 7.8% in a cohort where grafts were harvested from the femoral condyle. However, the study did not identify any significant gender-based differences. These discrepancies in findings may be attributed to variations in physical activity levels, pain thresholds, or psychological factors that influence postoperative recovery and symptom reporting. Considering these findings, our results lend support to the conclusion that gender is not a primary determinant of DSM or knee function outcomes. While some studies have suggested the presence of subtle differences in pain perception or subjective reporting, these factors do not appear to translate into significant functional disparities between male and female patients. This reinforces the overall reliability and safety of autologous osteochondral graft harvesting, regardless of gender.

Table 3. Correlation between the LKS at the follow-up and the clinical characteristics

Variables		LKS at the final follow-up
Age (years)	rho	0.028
	p-value	0.847
Weight (kg)	rho	-0.117
	p-value	0.415
Height (cm)	rho	0.074
	p-value	0.608
BMI (kg/m^2)	rho	-0.138
	p-value	0.332
Number of grafts (n)	rho	0.015
	p-value	0.915
Donor area (mm^2)	rho	-0.068
	p-value	0.634
Follow-up duration (months)	rho	0.138
	p-value	0.336

LKS: Lysholm knee score, BMI: Body mass index, rho: Pearson correlation coefficient

Table 4. Linear regression analysis predicting LKS at the final follow-up

Variables	B	S.E.	Beta	t	p
Constant	102,538	5,340		19,201	0.001
Age	0.082	0.060	0.254	1,365	0.179
Gender	-1.776	1,434	-0.210	-1.239	0.222
BMI	-0.192	0.151	-0.199	-1.277	0.208
Follow-up duration	0.028	0.028	0.173	0.997	0.324
Donor area	-0.035	0.035	-0.235	-1.003	0.321
Number of grafts	0.466	1,616	0.070	0.288	0.775
Defect filling	-1.280	1,731	-0.123	-0.740	0.464
R^2			0.103		
Adjusted R^2			-0.043		

LKS: Lysholm knee score, BMI: Body mass index, S.E.: Standard error, B: The column represents the unstandardized coefficient. Beta: The column represents the standardized coefficient

Higher BMI was not associated with poorer outcomes in our study, as both high and low BMI groups demonstrated similar LKS and functional recovery following osteochondral graft harvesting. This finding agrees with Andrade et al. (4), who conducted a systematic review and found no significant correlation between BMI and DSM in mosaicplasty procedures. Similarly, Guo et al. (18) reported that BMI did not significantly influence MRI-based cartilage quality or functional outcomes following graft harvesting. In contrast, other studies have suggested that elevated BMI may negatively impact DSM outcomes. Paul et al. (10) and Reddy et al. (14) observed poorer LKS and WOMAC scores in patients with higher BMI, attributing these outcomes to increased mechanical stress on the donor site during weight-bearing activities. The additional load on the knee joint in individuals with higher BMI may delay healing, increase inflammation, or accelerate degenerative changes at the donor site. Shimozono et al. (8) also noted a higher prevalence of DSM in patients with elevated BMI in their meta-analysis, suggesting that mechanical overload might contribute to donor site pain and functional limitations. Biomechanical studies support these findings by demonstrating increased contact pressures on the patellofemoral joint in individuals with higher BMI. Garretson et al. (20) reported that osteochondral defects in weight-bearing areas experience higher rim stress concentrations, which could lead to degenerative changes over time. This suggests that higher BMI might exacerbate stress-related degeneration at the donor site, particularly when larger grafts are harvested from high-load areas. The discrepancies in these results may be attributed to differences in study design, follow-up duration, and sample size. For instance, Matricali et al. (3) highlighted that smaller sample sizes and shorter follow-ups might fail to capture the long-term impact of BMI on DSM. Additionally, the location of graft harvesting might play a role, harvesting from areas with lower contact pressures, as suggested by Garretson et al. (20), may mitigate the negative effects of higher BMI. Our findings indicate that BMI may not universally affect DSM outcomes, particularly when graft harvesting is limited to small donor site areas and careful surgical techniques are employed. However, it remains essential to consider BMI as a potential factor during preoperative planning, especially for patients with elevated BMI who may require additional postoperative monitoring and weight management strategies to optimize recovery.

In our study, 91.2% of patients had one or two osteochondral grafts harvested, resulting in minimal DSM. This finding is consistent with Fraser et al. (16) and Nakagawa et al. (9), who reported no significant differences in knee function outcomes between single and double graft harvests. Similarly, Shimozono et al. (8) conducted a meta-analysis showing that DSM rates varied between 6.7% and 10.8%, depending on study size and follow-up duration. The relatively low morbidity rates associated with harvesting a limited number of grafts suggest that small donor site areas do not significantly impact knee function, especially when careful surgical techniques and appropriate donor site selection are employed. Donor site location is also critical in minimizing morbidity. Garretson et al. (20) demonstrated that harvesting from areas with lower contact pressures, such as the medial trochlea, can reduce the risk of degeneration and postoperative patellofemoral symptoms. Additionally, Andrade et al. (4) highlighted that DSM tends to be higher when grafts are harvested from high-load areas, such as the central

Table 5. Previous literature focused on DSM following autologous osteochondral graft harvesting from the knee

Author	Year	# patients	Follow-up (mean, months)	Outcome measure	Rate of DSM	Significant predictors of DSM
Reddy et al. (14)	2007	11	47	LKS	36.4% (4 out of 11 patients)	None identified
Iwasaki et al. (13)	2007	11	26	LKS, IKDC, MRI	0% reported, MRI shows fibrous repair	None identified
Paul et al. (10)	2009	112	55	WOMAC, LKS	Not specified numerically; higher BMI negatively influenced outcomes	Higher BMI, lower satisfaction
Nishimura et al. (7)	2010	12	24	LKS, VAS, muscle strength	No adverse effects on donor knee	Reduced extensor muscle strength at 3 months
Quarch et al. (15)	2014	37	Not specified	WOMAC, Tegner score, KSS, VAS	Up to 50%	Defects >3 cm^2
Fraser et al. (16)	2016	39	41.8	LKS, MOCART	12.5% at 24 months, 5% at final follow-up	Larger plugs lead to lower MOCART. No correlation between MRI findings and clinical outcomes
Nakagawa et al. (9)	2017	40	43.1	Knee symptoms, return to sport, radiological changes	15% (6 out of 40 patients)	None identified
Matsuura et al. (17)	2019	86	86	IKDC score, MRI findings	2.3% (usual), 12.8% (stricter)	Lower MOCART score
Guo et al. (18)	2022	46	98.3	LKS, MOCART	4.3% at 12 months, 0% at 24 months	None identified
Kurtuluş et al. (19)	2022	20	25.9	LKS, VAS, knee X-ray	20% (4 out of 20 patients)	Female, age >40 years, BMI ≥25, >1 graft
Current study	2024	52	36.2	LKS, knee X-ray	9.8% after 12 months	None identified

DSM: Donor site morbidity, LKS: Lysholm knee score, IKDC: International Knee Documentation Committee, MRI: Magnetic resonance imaging, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual analog scale, KSS: Knee Society Score, MOCART: Magnetic resonance observation of cartilage repair tissue

trochlea, compared to those from lower-load regions. These findings underscore the importance of strategic donor site selection to mitigate mechanical stress and optimize patient outcomes. In terms of managing donor site defects, our study found that filling the defect with a collagen membrane did not lead to improved functional outcomes. This observation aligns with Quarch et al. (15), who reported that TruFit plugs did not significantly enhance clinical results despite promoting defect regeneration. Fraser et al. (16) similarly found no correlation between synthetic plug integration and improvements in LKS. These results suggest that for smaller donor site areas, natural healing processes may be sufficient, and additional defect-filling interventions may not provide measurable benefits. Combining these insights, it appears that DSM can be effectively minimized by limiting the number of grafts harvested, selecting donor sites with lower contact pressures, and recognizing that defect-filling strategies may not always be necessary. These considerations collectively support the safety and efficacy of osteochondral autograft procedures when performed with meticulous surgical planning and technique.

This study has several strengths. First, it includes a relatively large sample size of 52 patients (57 knees), which enhances the robustness of our findings. The long follow-up period (mean of 36.2 months) allows for an in-depth evaluation of the progression and resolution of DSM over time. Additionally, standardized outcome measures such as the LKS provide a consistent framework for assessing knee function, facilitating comparison with other studies. Including various demographic and clinical parameters (e.g., age, gender, BMI, number and size of grafts, and defect filling) enables a comprehensive analysis of potential predictors of DSM.

Study Limitations

Our study also benefits from a rigorous statistical approach, including linear regression analysis, to identify independent predictors of DSM. However, this study also has some limitations. The retrospective design introduces the potential for selection bias and limits the ability to establish causal relationships. The relatively small number of cases with DSM (9.8%) may have reduced the statistical power to detect subtle differences or correlations. Additionally, while the follow-up period was sufficient to observe functional recovery, it may not have been long enough to identify late-onset osteoarthritic changes. The study's reliance on a single institution may also limit the generalizability of the findings. Finally, the subjective nature of patient-reported outcomes like the LKS may introduce bias related to individual pain perception or activity levels.

Conclusion

DSM following osteochondral graft harvesting from the knee is relatively low, with the majority of patients achieving excellent functional outcomes within one year. Our findings indicate that factors such as age, gender, BMI, the number and size of grafts, and defect filling do not significantly influence DSM. These results suggest that careful surgical technique, including limited graft harvesting and strategic donor site selection, can mitigate potential morbidity. The consistency of our findings with existing literature reinforces the safety and reliability of autologous osteochondral grafting as a treatment option for cartilage defects. Further prospective studies with larger sample sizes and longer follow-up periods are recommended to confirm these results and explore additional factors that may influence DSM.

Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee approved the study (approval number: 105, date: 08.11.2024).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.Ç.; Concept - A.A.; Design - A.Ç.; Data Collection or Processing - M.A.A., A.A.; Analysis or Interpretation - M.A.A., A.A.; Literature Search - M.A.A.; Writing - A.Ç.

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

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