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Investigation of the level of physical activity, coronavirus fear, and quality of life in oncology patients during the COVID-19 pandemic: A cross-sectional study

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Abstract

Background/Aim: There are no studies examining quality of life, anxiety levels, physical activities, and Covid-19 fear levels in people with cancer. The aim of this study was to examine physical activity status, coronavirus fear levels, and quality of life in oncological individuals during the COVID-19 pandemic.
Methods: This study was conducted among oncology patients. The level of physical activity was assessed using the Rapid Assessment of Physical Activity Scale (RAPA 1), the level of fear with the Fear of COVID-19 Scale (FCV-19S), and the quality of life with the COVID-19 Impact on Quality of Life Scale (COV19-QoLTR).
Results: The study was completed by 78 patients. Thirty-eight patients tested positive for COVID-19. Patients who tested positive for COVID-19 had significantly higher FCV-19S and COV19-QoL scores and lower scores of RAPA 1 (P<0.001). Also, FCV-19S was positively correlated with COV19-QoLTR and negatively correlated with RAPA 1 scores (P<0.001).
Conclusions: These findings suggest the need for more clarity and tailoring of physical activity-related advice for oncology patients with COVID-19 and improved support to resume activities important to individual well-being.

Keywords: cancer, COVID-19, fear, physical activity, quality of life

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Introduction

The coronavirus pandemic (COVID-19), a serious health problem worldwide, started with the detection of an epidemic of unknown etiology and severe viral pneumonia in the city of Wuhan, People's Republic of China, on 31 December 2019 [1]. It was subsequently found that the pathogen causing the development of this infection was an enveloped RNA beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. On 11 March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic due to the virus's frightening transmission rate and the severity of its symptoms [3]. The first case was announced in Turkey on 11 March 2020 [4].

According to the World Health Organization's COVID-19 reports, the adult COVID-19 patients in the Republic of China who died were mostly elderly people with chronic diseases [5]. In patients with a severe infection, chronic diseases were observed, such as cerebrovascular disease, chronic obstructive pulmonary disease, cardiovascular disease, and diabetes [6]. Apart from these comorbidities, the suppression of the immune system, which develops due to the treatment applied in oncological rehabilitation or due to the disease, is important as it can worsen the course of the COVID-19 disease. It has been reported that the clinical course of cancer patients with COVID-19 is worse than non-cancer patients, and the mortality rates are high [7]. In addition, it has been reported that the incidence and prevalence of COVID-19 infection are higher in individuals with oncological disease compared to other populations, and the presence of comorbidity increases the risk of COVID-19 infection with a more severe clinical picture [8]. Oncological patients are a highly vulnerable group, and mortality among patients with cancer with COVID-19 infection is approximately ten times greater than in the general population [7]. Moreover, patients receiving oncological treatment are in the risk group during the COVID-19 pandemic.

The COVID-19 pandemic has affected all humanity and patients receiving oncological treatment. Globally, 1.7 billion people (22% of the world's population) are at risk of severe COVID-19 infection, including 43 million common cancer cases [9]. The COVID-19 risk profile is affected by multiple parameters, including quality of life, fear, anxiety, depression, and physical activity in oncological patients. Reduced anxiety, depression symptoms, and enhanced physical function are important for oncological patients' health [10].

Although there are studies examining the quality of life, anxiety levels [10], physical activities [11], and COVID-19 fear levels [12] separately in people with cancer, no study has addressed all of these together. This study aims to examine the effect of the COVID-19 pandemic, which has had a significant impact on the world, on the physical activities, coronavirus fear levels, and quality of life of patients receiving oncological treatment.

Materials and methods

Sample size calculations

A statistical analysis program was used to perform the sample size calculations (G*Power package program, Ver. 3.1.9.2, Axel Buchner, Universitat Kiel, Germany). While determining the appropriate sample size for the study, the difference between the Fear of COVID-19 Scale scores in the study conducted by Sigorski et al. [13] in 2020 was considered. In the sample size analysis performed to obtain power with an effect size of 0.33, the number of participants was calculated as 69 with 5% type 1 error and 80% power.

Participants

Seventy-eight patients diagnosed with cancer and undergoing chemotherapy in oncology clinics older than 18 years were included in the study. We excluded patients who received psychological treatment had undergone surgery in the last 6 months, had additional physical disorders, and were inactive patients with high comorbidity. The patients were divided into two groups: Group 1: Oncology patients with COVID-19 disease (have SAR-Cov-2 positivity in their nasal or oral swabs) and Group 2: Oncology patients without COVID-19 disease.

Variables and outcomes

The demographic and clinical characteristics, medical management, quality of life, level of fear, and physical activity of the patients participating in the study were recorded. Data about age, gender, type of cancer, duration of treatment, and type of treatment were collected.

The COVID-19-Impact on Quality of Life (COV19-QoL) scale evaluated patients' quality of life. The Turkish version of the scale by Sümen et al. [14] is a reliable tool for assessing the impact of the COVID-19 pandemic on quality of life. Total scores are calculated by averaging the scores on all the items. A higher score indicates an increased impact of the pandemic on QoL. The Fear of COVID-19 Scale (FCV-19S), which is used to evaluate the effect of the pandemic process on psychological health, is a valid and reliable measurement tool. The Turkish version of the scale was developed by Satici et al. [15]. The Rapid Assessment of Physical Activity (RAPA) scale is a valid and reliable measure of physical activity. It comprised nine items related to different physical activities and participation in strength and flexibility training. The RAPA has two subscales: RAPA-Aerobic and RAPA-Flexibility and strength. The RAPA-Aerobic questionnaire is based on a scale of 1 to 7 measuring the amount, intensity, and duration of a person's physical activity. A score of greater than 6 indicates regular activity [16].

Statistical analysis

Statistical analyses were performed using SPSS, version 28.0 (Statistical Package for Social Sciences, (Armonk, NY: IBM Corp.). Continuous variables were presented by mean values (standard deviation), and categorical variables were presented as percentages. The conformity of the data to the normal distribution was examined with the Kolmogorov-Smirnov test. Non-parametric tests were used to analyze data that did not show normal distribution. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the Mann-Whitney test. The Spearman correlation analysis method was used for correlation analysis. *P*-value <0.05 was considered statistically significant.

Results

Seventy-eight patients who met the inclusion criteria were enrolled in the study. The demographics and clinical characteristics of the patients are summarized in Table 1. Patients in both groups were similar in age, gender, height, and weight. Table 1 shows the demographic and clinical characteristics of all patients.

Table 1: Demographics and clinical characteristics of the patients

		Group 1 (COVID-19+) n=38	Group 2 (COVID-19-) n=40	*P*-value
Sex- n(%)	Female	15 (39.5)	24 (60)	
	Male	23 (60.5)	16 (40)	0.070
Type of cancer-n(%)	Lung cancer	5 (13.2)	4 (10)	
	Breast cancer	14 (36.8)	9 (22.5)	
	Colon cancer	6 (15.8)	8 (20)	
	Gastric cancer	1 (2.6)	2 (5)	
	Other	12 (31.6)	17 (42.5)	0.622
Age (years)	Mean (SD)	60.44 (11.16)	57.79 (13.71)	0.252
Height(cm)	Mean (SD)	165.26 (20.35)	162.43 (15.89)	0.068
Weight (kg)	Mean (SD)	78.87 (20.68)	71.93 (22.72)	0.064
Type of treatment-n(%)	Inpatient	20 (52.6)	25 (62.5)	
	Outpatient	18 (47.4)	15 (37.5)	0.378

According to the results of these studies, FCV-19S and COVID-19-Impact on Quality of Life Scale (COV19-QoL) scores were significantly higher in Group 1 (whose COVID test result was positive) than in Group 2 (whose COVID test result was negative) (P<0.001). Additionally, in Group 1, RAPA scale scores were significantly lower than in Group 2 (P<0.001) (Table 2). Both groups had a moderate positive correlation between FCV-19S and COV19-QoL scale. Furthermore, a moderate negative correlation was found between FCV-19S and RAPA scores (Table 3). It has been observed that the fear of COVID-19 increases anxiety and depression, reduces the quality of life, and negatively affects physical activity.

Table 2: Comparison between the mean values of the scores of the COVID-19 Fear Scale, COV19-QoL and RAPA 1 scale between groups

	Group 1 (COVID-19+) n=38		Group 2 (COVID-19-) n=40			
	Med	**Min-Max**	**Med**	**Min-Max**	**Z score**	***P*-value**
COV19-QoL	4.00	(3 - 5)	2.00	1-5	6.711	<0.001
FCV-19S	23.00	(7 - 35)	10.00	(7 - 22)	7043	<0.001
RAPA- Aerobic	2.00	(1 - 6)	4.00	(1 - 6)	-4.642	<0.001

COV19-QoL: COVID-19-Impact on Quality of Life Scale, FCV-19S: The Fear of COVID-19 Scale, RAPA: Rapid Assessment of Physical Activity

Table 3: Correlations between FCV-19S, COV19-QoL and RAPA between the groups

		RAPA	**COV19-QoL**
Group 1 (COVID-19+) (n=38)	FCV-19S	R=-0.512	R=0.592
		P<0.001	*P*<0.001
Group 2 (COVID-19-) (n=40)	FCV-19S	R=0.529	R=-0.460
		P<0.001	*P*=0.003

COV19-QoL: COVID-19-Impact on Quality of Life Scale, FCV-19S: The Fear of COVID-19 Scale, RAPA: Rapid Assessment of Physical Activity

Discussion

In this study, we demonstrated the Fear of COVID-19 Scale (FCV-19S) and COVID-19-Impact on Quality of Life Scale (COV19-QoL) scores were significantly higher in Group 1, whose COVID test result was positive than Group 2. In addition, the Rapid Assessment of Physical Activity (RAPA) scale scores was significantly lower than in Group 2. The study has found that patients who receive oncological treatment, especially those who have COVID-19, should increase their physical activity, reduce their fear levels, and receive additional treatment and support to improve their quality of life.

With its extreme infection and mortality rates, COVID-19 is a global pandemic that is particularly dangerous for oncological patients [17]. Moreover, COVID-19 has been considered a determinant of fear, stress, anxiety, and mood disorders and negatively impacts people's physical health and, consequently, their quality of life [18]. Our study found that oncology patients with COVID-19 had higher COVID-19-QoL scores. The first finding could indicate a possible recovery pattern similar to that which has been established in COVID-19 infection, where the patient experience impaired quality of life and a poor health-related quality of life [19]. The second could be chemotherapy treatment. Which is comprehensive of both mental and physical health-related as well as the quality of life

There is a lack of data on cancer patients' fear and anxiety related to COVID-19. A variety of tools and questionnaires were suggested to measure patient anxiety. FCV-19S was designed by Ahorsu et al. [20]. Subsequently, it has been validated in many nations, becoming one of the most widely used instruments for evaluating COVID-19 for anxiety. We showed that FCV-19S had higher scores compared to oncological patients with COVID-19. For oncological patients, many triggers might cause worry. Nevertheless, cancer itself seems to be the most significant factor. Aside from the risk of infection, the impact of COVID-19 on cancer care appears to have exacerbated patients' emotions of disease and isolation, resulting in a deterioration in these patients' COVID fear.

Most cancer organizations recommend that oncological patients exercise for 150 min (aerobic, moderate to high-intensity physical activity) each week [21]. The best type or domain of physical activity for oncological patients is unclear [22]. It is common for patients with cancer to feel depressed and physically inactive.

Physical inactivity and prolonged sitting are highly prevalent among oncological patients, especially due to chronic symptoms such as fatigue, pain, and muscular weakness. Furthermore, self-isolation measures among oncological patients are also a concern; clinicians have traditionally urged patients to rest and refrain from physical activity. Humphreys et al. have shown the challenges of regulating physical activity alongside the extended symptoms associated with long COVID-19 [23]. A possible interpretation of these interrelated factors is that increased feelings of fatigue associated with cancer may complicate activities of daily living.

The findings of this study should be evaluated with some limitations in mind. First, the study used self-reported questionnaires, which may raise the concern of common method bias. In addition, the patients differed in duration and type of cancer treatment; we could not completely account for the patient's preexisting medical conditions before the COVID-19 infection. Studies in the future can focus on COVID-19 poses an imminent and obvious risk to physical health.

Conclusions

Oncological patients must be considered at risk of substantial distress when operations, chemotherapy treatments, and follow-up visits are postponed due to interrupted healthcare infrastructure. For this reason, it is critical to take care not only of the physical but also of the mental health of oncological patients. In addition, physical activity should be recommended to

oncological patients to maintain physical function and quality of life.

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Research article

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Cuffed-tunneled catheters in hemodialysis patients: problems and solution methods: A single-center retrospective cohort study

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Ethics Committee Approval
Ethical approval was obtained from Adıyaman University Non-Invasive Clinical Research Ethics Committee (date: 21/09/2021, number: 2021/07-31).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Cuffed-tunneled catheter patients encounter various problems during their catheterization period. Early detection and resolution of these problems prolong the life of the catheter. The purpose of the present study was to investigate the problems and solution methods of cuffed-tunneled catheters in hemodialysis patients during their use in light of our experience and literature.

Methods: The study was designed as a retrospective cohort study. Twenty-four months of patient data who had a diagnosis of renal failure and who received cuffed-tunneled hemodialysis catheters between January 2013 and June 2021 in the Department of Cardiovascular Surgery of Adiyaman University Faculty of Medicine were analyzed electronically based on the hospital data recording system. The demographic characteristics, localization of the inserted catheter, and duration of catheter use were determined. Primary and secondary patency ratios were calculated and recorded along with the complications in the patients and our treatment approaches to these complications. Finally, the collected data were discussed with reference to the literature data.

Results: The data from 322 cuffed-tunneled catheters were collected in a total of 228 patients during the observation period. It was found that no revision procedure was applied to 73 patients (catheter) during the 24-month period, and a total of 204 revision procedures were applied to 155 patients. The revision procedure consisted of 110 thrombolytic treatments, 64 vein exchanges, 18 tunnel changes, and 12 catheter changes. Primary and secondary patency ratios at 6, 12, 18, and 24 months were calculated as 90.79%, 63.60%, 40.11%, and 32.02% and 96.05%, 89.91%, 72.37%, and 58.33%, respectively. The most common factors that affected primary and secondary patency ratios were determined to be gender ($P<0.001$ and $P=0.056$, respectively), body mass index ($P<0.001$ and $P<0.001$, respectively) and diabetes mellitus ($P=0.018$ and $P=0.690$, respectively).

Conclusion: Thrombolytic treatment is an effective and safe method in catheter thrombosis, which is one of the most important factors rendering the cuffed-tunneled hemodialysis catheters dysfunctional. Also, in tunnel infections, tunnel replacement is a salvage procedure in patients with vascular access problems.

Keywords: hemodialysis, cuffed-tunneled hemodialysis catheters, catheter thrombosis, patency ratios

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Introduction

Tunneled hemodialysis catheters (THC) have been produced with various designs since 1985 and have been used to present day due to ease of placement and use. They can be cuffed or uncuffed and constructed with polyurethane or silicone. In general, hemodialysis catheters act as a temporary bridge in dialysis-dependent patients until the time required for a permanent vascular access pathway, such as an arteriovenous fistula, to mature is complete. Indications to gain permanent access in patients with previously used permanent vascular access dysfunction or vascular access site depletion are usually present. They are produced in appropriate diameters and shapes to provide extracorporeal blood flow of 300 to 400 ml/min, which is necessary for an effective dialysis procedure [1,2].

During their usage period, all central venous catheters are subject various complications, which include immediate mechanical complications associated with insertion procedures or late complications, such as catheter-related infection, and longer-term complications, such as central vein thrombosis, catheter thrombosis, and fibrin sheath. The rates of procedure-related complications, such as catheter malposition, pneumothorax, arterial injury, arrhythmia, and venous air embolism, decreased considerably after the routine use of ultrasound guidance [2,3].

Although catheters can be placed in all central veins, the contralateral internal jugular vein (such as right internal jugular vein because of anatomical compatibility) should be preferred initially so that it does not affect the arteriovenous fistula that has been (or will be) created [4].

The purpose of the present study was to retrospectively examine the cuffed-tunneled catheters placed for hemodialysis in our cardiovascular surgery clinic, to examine related complications, insertion techniques, and factors that affect primary and secondary catheter patencies and to share our experience in the light of the literature data.

Materials and methods

The study was designed as a retrospective cohort study and was initiated after the approval of the Non-Interventional Ethics Committee of Adiyaman University on 21/09/2021 with the decision number 2021/07-31. The data were collected in a digital medium using the patient data recording system. The data of patients who were referred to our Cardiovascular Surgery Clinic from the Nephrology Clinic between January 2013 and June 2020 and received a cuffed-tunneled hemodialysis catheter were analyzed. The patients who had two-year follow-up data were included in the study. Demographic data, catheter localizations, complications, and treatment approaches to these complications were determined from the file scan. Primary and secondary patency ratios of the catheters and factors that affected the patency ratios were recorded.

Definitions

Primary Patency Ratio: The primary patency ratio reflects the time from the insertion of the catheter to the first intervention for the same catheter. The initial intervention includes thrombolytic treatment, mechanical thrombectomy, and/or removal of the fibrin sheath [5].

Secondary Patency Ratio: The secondary patency ratio defines the time from the insertion of the catheter to the replacement or removal of the same catheter for any reason [5].

Infection Rate: The infection rate per 1000 catheter days=(the number of infected catheters)/(the total number of catheters X follow-up time) x 1000 [1].

Interventional Procedure: All procedures were performed on patients in the supine position in a sterile operating room setting. The patient was placed in the Trendelenburg Position for placement of the internal jugular and subclavian vein catheters. Local anesthesia was administered with a 22G tip injector after the area in which the catheter was placed was cleaned with povidone-iodine, and the patient was covered. The patient was positioned in the Slight Trendelenburg Position, facing the opposite side for the internal jugular vein (IJV) preferences. The puncture was performed from the top of the triangle, which was formed by the lateral and medial legs of the sternocleidomastoid muscle [6]. The artery was palpated with the other hand during the puncture and entered from the lateral side of the finger from which the pulse was taken. A 22G tip injector was used for the puncture. In this way, the formation of hematoma in possible arterial punctures was prevented. The IJV was punctured with a 10 Fr catheter insertion needle after the vein tracing was fixed with a 22G injector.

A direct catheter needle was used for a puncture in the subclavian vein (SCV) preferences because a 22G needle may be short after local anesthesia. Technically, the vein was punctured by stripping the bottom of the clavicle from the mid-lateral one-third point of the clavicle and advancing the needle horizontally towards the sternal notch or the opposite shoulder [6]. The guide wire was sent from the catheter needle to the vein lumen and the guide-wire entry site was enlarged with an incision of approximately 3 mm. The appropriate catheter length was calculated for the patient. The length between the third intercostal space (with the tip of the catheter at this point), the skin entry site of the guide wire, and the cuff of the catheter was marked. The skin entry area of the cuff was adjusted to be approximately 2–3 cm proximal over the breast. The catheter was passed through the subcutaneous tissue with the tunneler and the guide wire was removed from the entry area. The dilatator and the peelable sheath were inserted into the vein lumen using circular movements over the guide wire. The lock mechanism was opened with the Valsalva Maneuver, and the guide wire and dilatator were removed from the sheath. The catheter was directed through the sheath of the previously measured size. The sheath was removed from both sides. The catheter lumen was rinsed with heparinized fluid. The tunnel was fixed close to the exit site to prevent the cuff from exiting the skin, and a suture was placed on the skin so that it would not impede the catheter.

As the target vein, the right IJV was preferred. However, if the right IJV region was not suitable because of multiple interventions, left IJV, right SCV, or left SCV was the preferred vein for catheter localization. The lengths of the catheters used for the upper central veins were 19–28 cm, self-curved and constructed of silicone/silastic according to the condition of the patient.

Femoral veins were preferred in patients whose upper extremity venous structures were depleted or unsuitable.

Although similar in terms of the procedure and technique, the selected catheters were also in silicone/silastic structure and their lengths were between 27 and 35 cm (between tip and cuff).

Creating A New Tunnel: Creation of a new tunnel is a method that preserves the existing venous access route in patients who have minimal symptoms, catheter tunnel, or exit site infection. Local anesthesia was applied to the venotomy site after the standard skin and catheter site are prepared and covered with the povidone–iodine scrub. A small incision was made to access the catheter. The catheter was transected, and the peripheral tip was removed and discarded. A guide wire was sent from the segment of the catheter in the vein. The old catheter was removed and discarded so that it does not touch the surgical field. The guide wire in the vein was wiped with sterile saline and an antiseptic solution. The surgeon changed sterile gloves. A new exit point and tunnel were then created in a suitable area lateral to the first tunnel. The new catheter was passed through the new tunnel and tunneled to the old venotomy site using the standard technique [7].

Thrombolytic Treatment with Alteplase: The procedure was performed in the intensive care unit under patient monitoring. Five ml (5 mg) of Alteplase was administered into each lumen of the thrombosed catheters, and this process was repeated three times at an interval of half an hour. After this procedure, which was applied at 0, 30, and 60 min, the patient was followed for about half an hour. The administered dose was as much as the recommended accelerated loading dose for acute myocardial infarction [8]. The patients who did not develop complications were followed in the ward.

Statistical analysis

Statistical analyses were performed using Graphpad Prism 8.0.2 (La Jolla, CA: Retrieved from GraphPad Software, Inc. http://www.graphpad.com/scientific-software/prism/). The survival rate of the catheter was calculated using the Kaplan–Meier analysis. The conformity of the variables to the normal distribution was evaluated with the Kolmogorov–Smirnov analysis. The homogeneity of the variances was evaluated with Levene's Test. Nonparametric data were compared by using the Mann–Whitney U-test. The equality of survival profiles between patients with and without potential predictors of thrombosed catheters was examined using the log rank test. The Multivariate Regression Analysis was used for the predictors of the Patency Ratios. The categorical variables were compared by using the chi-squared Test. Results are presented as mean values (standard deviation) and the comparisons with a *P*-value below 0.05 were considered significant.

Results

It was determined that 322 cuffed-tunneled catheters were placed in 228 patients. The mean age of the patients was 59.92 (8.52) at the time of the procedure. Among the patients, 36.40% were female, and 63.60% were male. The demographic data of the patients are given in Table 1. The right internal jugular vein (RIJV) with 104 (45.61%) catheters was the most common venous access route. It was understood from the file scan that 50 (21.93%) catheters were inserted into the right subclavian vein (RSCV), 32 (14.03) into the left subclavian vein (LSCV), 14 (6.14%) into the right femoral vein (RFV), and six (2.63%) into the left femoral vein (LFV) as shown in Table 1.

Table 1: Demographic data of the patients during the follow-up period

	Revised catheter n=155	Unrevised catheter n=73	*P*-value
Age of follow-up means (SD)	60.05 (8.86)	58.6 (7.64)	0.018[a]
Gender n(%)			
Male	92(59.36%)	53(72.60%)	<0.001[a]
Female	63(40.64%)	20(27.40%)	
BMI	27.57 (4.36)	21.93 (3.32)	<0.001[a]
CRF etiology n(%)			
HTN	49 (31.61%)	23 (31.51%)	0.987[b]
DM	81(52.26%)	41 (56.16%)	0.581[b]
GLN	5 (3.22%)	1 (1.37%)	0.414[b]
PRD	5 (3.22%)	1 (1.37%)	0.414[b]
VASC	31 (20%)	13 (17.81%)	0.410[b]
DRG-IN	2 (1.3%)	3 (4.11%)	0.175[b]
Unknown	24 (15.48%)	10 (13.70%)	0.724[b]
Use of drug n(%)			
Acetyl salicylic acid	49 (31.61%)	26 (35.62%)	0.548 [b]
Clopidogrel	22 (14.19%)	10 (13.70%)	0.920 [b]
Antihypertensive	54 (34.84%)	33 (45.21%)	0.133[b]
Beta-blocker	69 (44.52%)	44(60.27%)	0.026 [b]
Access zone n(%)			
RIJV	56 (36.13%)	48 (65.75%)	0.001[b]
LIJV	17 (10.97%)	5 (6.85%)	
RSCV	40(25.81%)	10 (13.70%)	
LSCV	22 (14.19%)	10 (13.70%)	
RFV	14 (9.03%)	0(0%)	
LFV	6 (3.87%)	0(0%)	

CRF: Chronic renal failure, HTN: Hypertensive nephropathy, DM: Diabetes mellitus, GLN: Glomerulonephritis, PRD: Polycystıc renal dısease, VASC: Vasculitis, DRG-IN: Drug İnduced, RIJV: Right internal jugular vein, LIJV: Left internal jugular vein, RSCV: Right subclavian vein, LSCV: Left subclavian vein, RFV: Right femoral vein, LFV: Left: femoral vein, SD: standard deviation, a: Mann–Whitney U test, b: Chi-squared test

It was found that all catheters were placed by one single surgical team. Routine ultrasound (USI)-guided catheter placement was not performed because of difficulties in accessing USI, and catheters were placed in only four (1.75%) patients under USI guidance (multiple catheter intervention or obese patient).

It was found that no revision was applied to 73 patients during the two-year follow-up period, and a total of 204 revisions were performed on 155 patients. It was also understood from the file scan that the most common revision procedure was the application of thrombolytic treatment with Alteplase to 99 catheters, 110 times, in addition to revision procedures (64 vein exchanges, 18 tunnel changes, and 12 catheter changes). Also, it was found in the file that 11 patients had been treated with thrombolytic treatment twice at different times (Table 2). The most common complication was catheter thrombosis (43.42%) followed by 27% catheter-associated infection (1.37% infection rate per 1000 catheter days) and 7.89% tunnel infection (0.11 infection rate per 1000 catheter days). Other complications and their rates are summarized in Table 2.

Primary patency ratios of the catheters in the sixth, 12th, 18th, and 24th months were calculated as 90.79%, 63.60%, 40.11%, and 32.02%, respectively, and secondary patency ratios were 100%, 89.91, 72.37, and 58.33%, respectively (Figure 1). Multivariate logistic regression analysis was used to determine the factors that affected the primary and secondary patency ratios of the catheters (Table 3). According to this analysis, a significant regression model was found for the primary dependent variable, F(10, 216) 24.21, P<0.001, and 51% of the variance in the variable (R^2 adjusted=0.51) was explained by the independent variables. In this respect, the gender independent variable predicted the primary dependent variable positively and significantly, body mass index (BMI) predicted the primary dependent variable negatively and significantly, diabetes predicted the primary dependent variable negatively and

significantly, the localization predicted the primary dependent variable negatively and significantly ([ß=–0.179, t [216]=3.62, *P*<0.001, pr2=0.057], [ß=–0.548, t[(216]=–10.846, *P*=0.012, pr2=–0.292], [ß=–0.114, t[216]=–2.376, *P*=0.018, pr2=–0.0256], and [ß=–0.177, t[216]=–3.079, *P*=0.002, pr2=0.042, respectively]). Also, a significant regression model in the multivariate linear regression analysis that was constructed to predict the secondary dependent variable using independent variables showed that F(10, 216) 8.762, *P*<0.001, and 26% of the variance (R^2 adjusted 0.26) in the second dependent variable was determined by the independent variables. In this respect, BMI predicted the secondary dependent variable as negative and significant, localization predicted the secondary dependent variable as negative and significant ([ß =–0.308, t[216]=–4.962, *P*=0.012, pr2=0.1024] and [ß=–0.322, t[216]=–4.557, *P*<0.001, pr2=0.088, respectively]). As a result of this analysis, BMI and localization were found to be the factors that affected both primary and secondary patency ratios, and female gender and the presence of diabetes significantly affected primary patency ratios (*P*<0.001 and *P*=0.018, respectively) as shown in Table 3. Primary and secondary patency rates according to localization in diabetic patients are summarized in Table 4.

Table 2: Complications and revision procedures

Procedural	n (%)
Bleeding	2 (0.88%)
Pneumothorax	1 (0.44%)
Arrhythmia	17 (7.45%)
Malposition	2 (0.88%)
Air embolism	5 (2.19%)
Catheter dysfunction n (%)	
Thrombosis	91 (39.91%)
Fibrin sheath	13 (5.70%)
Central vein stenosis	11 (4.82%)
Catheter-related infection n (%)	
Catheter-related blood infections	42 (18.42%)
Tunnel infection	18 (7.89%)
General complications n (%)	
Deep venous thrombosis	7 (3.07%)
Pulmonary embolism	2 (0.88%)
Limb ischemia	4 (1.75%)
Revision procedures n	
Thrombolysis with alteplase*	110
Vein exchange	64
Change of tunnel	18
Change of catheter	12

* Thrombolysis was applied to 11 catheters twice at different times.

Table 3: Multivariate regression analysis to identify predictors of primary and secondary patency rates

Variables	Beta	t	*P*-value	95.0% CI for B		Correlations		
				Lower	Upper	Zero-order	Partial	Part
Age Primary	-0.002	-0.028	0.978	-0.099	0.096	–0.171	–0.002	-0.001
Secondary	0.035	0.515	0.607	-0.067	0.115	–0.163	0.035	0.030
Gender Primary	0.179	3.625	0.000	1.300	4.396	0.358	0.239	0.169
Secondary	0.116	1.923	0.056	-0.036	2.858	0.255	0.130	0.110
BMI Primary	-0.548	-10.85	0.000	-1.556	-1.077	–0.663	–0.594	-0.507
Secondary	-0.308	-4.962	0.000	-0.786	-0.339	–0.421	–0.320	–0.285
DM Primary	-0.114	-2.376	0.018	-3.197	-0.298	–0.195	–0.160	–0.111
Secondary	-0.023	-0.399	0.690	-1.628	1.080	–0.086	–0.027	–0.023
HT Primary	-0.003	-0.053	0.957	-1.626	1.540	–0.015	–0.004	-0.002
Secondary	0.045	0.746	0.456	-0.919	2.039	0.010	0.051	0.043
GLN Primary	-0.050	-1.045	0.297	-6.846	2.103	-0.060	–0.071	-0.049
Secondary	0.067	1.148	0.252	-1.747	6.615	0.050	0.078	0.066
PRD Primary	-0.040	-0.821	0.412	-6.517	2.683	–0.135	–0.056	-0.038
Secondary	0.035	0.590	0.556	-3.012	5.584	–0.063	0.040	0.034
VASC Primary	-0.073	-1.506	0.134	-3.150	0.421	–0.053	–0.102	-0.070
Secondary	-0.039	-0.656	0.512	-2.224	1.113	–0.027	–0.045	-0.038
DRG-IN Primary	0.004	0.082	0.935	-5.235	5.688	–0.009	0.006	0.004
Secondary	-0.027	-0.463	0.644	-6.302	3.904	–0.057	–0.031	-0.027
LOC Primary	-0.177	-3.079	0.002	-1.540	-0.338	–0.377	–0.205	-0.144
Secondary	-0.322	-4.557	0.000	-1.860	-0.737	–0.400	–0.296	-0.262

BMI: Body Mass Index, DM: Diabetes mellitus, HT: Hypertension, GLN: Glomerulonephritis, PRD: Polycystıc renal dısease, VASC: Vasculitis, DRG-IN: Drug induced, LOC: localization, CI: confidence interval

Both primary and secondary patency ratios were found to be higher in non-diabetic patients based on the Kaplan–Meier analysis between diabetic and non-diabetic patients (Figure 2). Based on the Kaplan–Meier analysis that was constructed according to gender, primary (*P*<0.001) and secondary (*P*=0.002) patency ratios were found to be high in males (Figure 3). During the two-year follow-up, the primary patency rates for the 64 patients (followed for 12 months) who underwent thrombolytic therapy with Alteplase at three, six, nine, and 12 months were 95.31%, 81.25%, 70.31%, and 53.13%, respectively (Figure 4).

Table 4: Primary and secondary patency rates by localization in diabetic patients

Time (month)		RIJV	LIJV	RSCV	LSCV	RFV	LFV
6	**Primary**	98.11	88.89	78.26	82.61	55.56	20
	Secondary	100	100	100	100	100	5-100
12	**Primary**	64.15	55.56	39.13	52.17	0	0
	Secondary	98.11	100	59.56	82.61	77.78	60
24	**Primary**	56.60	22.22	17.40	26.09	0	0
	Secondary	86.68	66.67	43.48	47.83	0	0

Figure 1 : Primary and secondary patency rates independent of risk factors

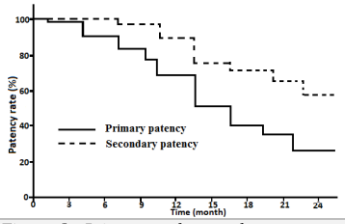


Figure 2: Primary and secondary patency rates in diabetic and non-diabetic patients

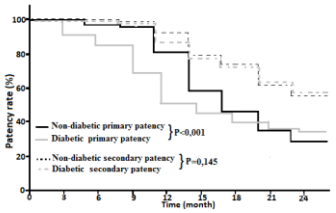


Figure 3: Primary and secondary patency rates of catheters by gender

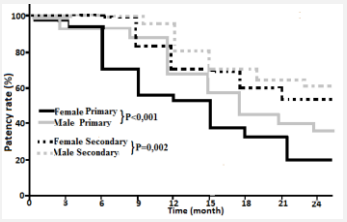


Figure 4: 12-month primary patency rates in patients undergoing thrombolytic therapy with Alteplase

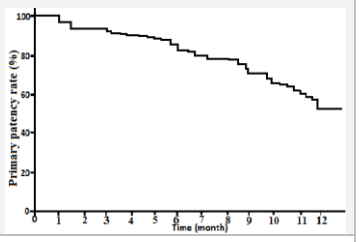
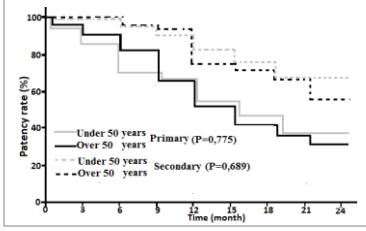


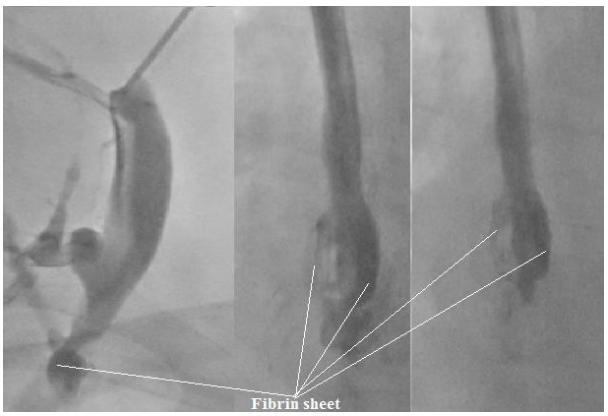
Figure 5: Primary and secondary patency rates in patients younger than and over 50 years old



It was observed that age did not affect the primary and secondary patency rates. Patency rates of patients under 50 and over 50 years of age are shown in Figure 5.

Fibrin sheets were detected in 13 patients who underwent thrombolytic treatment (Figure 6). It was determined that no problems in the routine dialysis of these patients after the procedure existed.

Figure 6: Fibrin sheet



Discussion

Arteriovenous fistulas are the best vascular access routes for patients whose life depends on hemodialysis. However, tunneled hemodialysis catheters are the best alternative for patients who have a history of multiple failed fistula attempts [9]. A recent study argued that approximately 80% of patients who had renal failure would require hemodialysis catheters at some point in their lives. The current National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations indicate that the RIJV is the preferred insertion site for THC because of its more linear route compared to the left side [10].

Although IJVs are generally preferred for tunneled catheter placement, SCVs are preferred less frequently. SCVs are not generally preferred because they eliminate the chance of central vein thrombosis and fistula opening in the ipsilateral upper extremity and/or graft [9].

Although the use of USI during catheterization was recommended (Level of Evidence B), its routine use has not been established yet. Also, it was shown that blind catheter placement without the use of USI can reduce complications if it is performed repetitively by the same surgical team [11,12]. In the current study, no serious complications related to the procedure developed in the series except pneumothorax in one patient and malposition in two patients out of 228 patients. We associate this result with the fact that all catheter procedures were performed by the same surgical team.

Although THCs provide the clinician with a chance for immediate vascular access, several factors limit their use and affect their survival. Those factors related to the placement procedure include catheter-related bloodstream infections, catheter thrombosis, and venous thrombosis [2]. For these complications, catheter-saving or venous access-saving interventions are important in terms of preserving the already limited venous access tract in patients. In this context, a chance for intervention must be given to every dysfunctional catheter. Thrombolytic treatment with alteplase was used in our series in acute thrombosis of the catheter and venous access route. In the United States, Alteplase is currently used in the standard treatment of catheter thrombosis [13]. No additional complication was detected in any of our patients with this application. A total of 110 thrombolysis protocols were performed on 99 catheters. Primary patency ratios at three, six, nine, and 12 months were 95.31%, 81.25%, 70.31%, and 53.13%, respectively, of the 64 patients who were followed up for 12 months and underwent thrombolytic treatment with alteplase. These rates can be considered quite successful in the patients for whom the protection of the venous access route is very important.

Catheter or tunnel infections are another cause of catheter or venous access route losses [2]. Catheters can become occluded secondarily to a thrombotic process (such as the fibrin sheath around the catheter tip or an intra-luminal blood clot). A fibrin sheath is one of the most common causes of thrombotic obstruction. It can occur within 24 h of catheter insertion and usually develops within two weeks. The fibrin sheath usually does not affect catheter function, but may create a one-way valve on the catheter tip, causing partial occlusion. The negative pressure created when attempting to aspirate blood creates a suction that pulls the fibrin sheath over the catheter tip, preventing blood from being withdrawn. The blockage dissolves when negative pressure is eliminated (such as during infusion or catheter flushing), allowing fluids to pass through easily with THC. Although a fibrin sheath usually does not cause any clinical symptoms, a slight risk of embolization of the fibrin material is present [13].

In the population of the present study, a fibrin sheath was detected in 13 patients. Full patency was achieved in all patients in our thrombolytic treatment procedure, which was performed with Alteplase at an interval of half an hour. No problems were detected in the following dialysis sessions.

Catheter-related blood infection was observed in 42 patients and tunnel infection was observed in 18 patients in the current study. Antibiotic treatment and catheter and vein replacement were required according to the results of the culture antibiogram in blood infections. The vascular access route was preserved in tunnel infections and tunnel replacement was performed.

Diabetic patients have a high risk for catheter-related thrombosis [14]. In the present study, when primary and secondary patency ratios were examined according to localization in diabetic patients, the one-year primary patency ratio was the highest in terms of RIJV (64.15%), and the lowest was in terms of the RSCV. The one-year secondary patency ratio was highest in the left internal jugular vein at 100%. Based on these results, the first preferred venous access site in diabetic or non-diabetic patients must be the internal jugular veins. Ideally, the catheter must be placed on the opposite side of the planned or maturing arteriovenous fistula (AVF). Subclavian veins must be avoided whenever possible because of the risk of venous stenosis and AVF compromise. Femoral veins are less preferred because of low catheter survival, deep vein thrombosis, and related complications [15, 16]. Internal jugular veins were preferred most frequently and subclavian veins were the preferred second choice in the current study. The femoral vein region was used to increase the chance of survival in obese patients and patients with upper vein depletion.

The primary and secondary patencies of the catheters provide a wide range of variations, ranging from 25% to 75% per year. This range variation is probably due to the lack of aseptic environment maintenance, level of general catheter care, management level of catheter dysfunction, and treatment of infection [16]. In our series, the one-year primary patency ratio of the catheters was 63.60%, and the secondary patency ratio was 89.91%, which was above values in the literature. We think that the insertion and follow-up of all catheters by a single surgical team is the most important reason for this high rate.

Catheters sometimes rupture at the insertion site because of their manipulation during dialysis. In such a case, the catheter must be changed by maintaining the venous access route [17].

Limitation

The only limitation of our study is its retrospective nature.

Conclusion

Catheter and vein-sparing procedures must be tried in hemodialysis patients whose vascular access path is very important and limited. Especially, thrombolytic treatment in catheter thrombosis and tunnel replacement, which is a vein-sparing method in tunnel infections, are the methods that can be used.

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Immunohistochemical study of CD147 and matrix metalloproteases in meningiomas

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Abstract

Background/Aim: Expression of extracellular matrix proteins and metalloproteases (MMPs) has been implicated in neoplasm recurrence. Some recent studies have suggested a correlation between matrix modifier proteins and recurrence or invasion of meningiomas. Based on previous data, the aim of this study was to find a correlation between the immunohistochemical (IHC) expression patterns of a group of matrix modifier proteins, including CD147, Matrix Metalloprotease 2 and 9 (MMP2 and 9, respectively), Epithelial Cadherin (ECAD), and Galectin-3 (GAL3) with World Health Organization (WHO)-defined grade, brain invasion, recurrence, and other clinicopathological features.
Methods: This study was a cohort study. All patients with meningioma who underwent resection over a 10-year period were identified from the electronic pathology archives. Tissue microarrays (TMAs) were created for IHC studies, and IHC staining was performed using standard methodology.
Results: A total of 231 cases fulfilled the study criteria. Histological review identified 198 grade 1 tumors (85.3%), 28 grade 2 tumors (12.6%), and five grade 3 tumors (2.2%). CD147 was determined to be positively correlated with WHO-defined grade (P=0.009). ECAD, MMP2, MMP9, GAL3 were not found to be correlated with brain invasion, recurrence, or WHO grade.
Conclusion: The study results demonstrated that CD147 could be a target for diagnosis, prognosis, and treatment of meningiomas.

Keywords: meningioma, CD147, matrix metalloproteases, MMP2, MMP9, galectin-3, E-cadherin, immunohistochemistry

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Introduction

Meningiomas are the most common primary extra-axial central nervous system (CNS) tumors in adults and are thought to arise from arachnoid cells. According to the World Health Organization (WHO) 2016 criteria [1], meningiomas are classified as grades 1 through 3 corresponding to increasing recurrence risk and decreasing survival probability. WHO grade 1 meningiomas represent approximately 85% of all meningiomas and show several histological variants. WHO grade 2 represents approximately 5%–7% of all meningiomas and include the atypical, clear cell, and chordoid variants. WHO grade 3 meningiomas constitute 3% of all meningiomas and include anaplastic, papillary, and rhabdoid variants [2]. Histological grade is currently one of the most important prognostic factors. The local recurrence rate has been reported as 50%–78% for Grade 3 anaplastic meningiomas, 29%–40% for grade 2 atypical meningiomas, and 7%–20% for grade 1 meningiomas [2,3].

Extracellular matrix (ECM) proteins, metalloproteases (MMPs), and their modifier, CD147, have been implicated in many physiological and neoplastic processes, such as cell adhesion, cell migration, embryonic development, wound healing, hemostasis, oncogenic transformation, angiogenesis, and metastases and in the recurrence and invasiveness of many tumors [4]. MMPs, cadherins, especially E-cadherin (ECAD), and lectins, such as galectin-3 (GAL3) are the critical members in this group of molecules [5]. Some authors suggested that overexpression of fibronectin and GAL3 in meningiomas [6] may be associated with aggressive tumor behavior in meningiomas [7,8]. Loss of ECAD was identified in several neoplasms including meningiomas, and has been associated with tumor invasion [9,10]. In other studies, expression levels of ECAD and beta-catenin were shown to inversely correlate with invasion and recurrence of meningiomas [11]. Some studies suggested that malignant tumors express MMPs at higher levels than benign tumors although the reason and mechanism for this expression is not clear [12–15]. CD147 is a membrane glycoprotein expressed at varying levels in many cell types [16]. CD147 stimulates peritumoral fibroblasts to secrete MPPs and promotes invasiveness of various malignant tumor cells, including liver, prostate, skin, bladder, lung, and breast and was also reported in meningiomas [17]. High expression of CD147 on cancer cells was found to be positively related to cancer progression and poor prognosis [18].

The overall balance of MMPs appears to play a central role in many physiological and pathological processes. MMPs and CD147 are considered to be promising targets for cancer therapy, and so far, some synthetic and natural MMP inhibitors have been identified. However, therapeutic approaches aiming to block MMPs have not yet been successful in the treatment of cancer patients.

This study was undertaken to determine whether the matrix modifying proteins and CD147 previously associated with the behavior of meningiomas also correlate with the WHO-defined grade and hence aggressive behavior, and whether this relationship is strong enough to be relevant for clinical application.

Materials and methods

Ethics committee approval for the study was obtained from 19 Mayıs University Medical School (B.30.20DM.0.20.08/2013). This study was conducted in accordance with the Declaration of Helsinki and designed as a cohort study. Patients diagnosed with meningioma at 19 Mayıs University Medical School Hospital between 2002 and 2012 were identified based on the electronic pathology archives. The available clinical information was obtained from the electronic medical records and archived patient charts. The inclusion criteria for the study included two parameters: 1) patients with sufficient pathology material and 2) patients with the minimum necessary clinical information. Exclusion criteria were defined based on several parameters: 1) re-excision specimens, 2) patients with insufficient clinical information or pathology material, and 3) pathological diagnosis other than meningioma. All sections stained with hematoxylin and eosin (H&E) were reviewed to confirm the diagnosis of meningioma. A histological review was performed by two pathologists, and a consensus diagnosis was recorded in all cases. Each case was evaluated according to the 2016 WHO criteria and was assigned a grade and a histological type. For immunohistochemical (IHC) studies, tissue microarrays were created. IHC staining for MMP2 (PA1-16667 Thermo Fisher Scientific, 1:250), MMP9 (PA1-38182 Thermo Fisher Scientific, 1:250), ECAD (Zymed clone HECD-1; 1:100), GAL3 (Santa Cruz clone sc-32790; 1:50), epithelial membrane antigen ([EMA] Leica clone Gp1.4; undiluted), CD34 (QBEND/10, Leica; prediluted), and extracellular matrix metalloproteinase inducer (EMMPRIN)/CD147 (C-19, Santa Cruz Biotecnology, 1:50) was performed using standard methodology. CD34, EMA, and S100 protein values were used to confirm the diagnosis. The staining was interpreted in comparison with the positive controls, and the scoring was performed using a three-tiered scale: (1) 0: negative, (2) 1: focal or weak staining, and (3) 2: strong diffuse staining. Focal or weak staining implied staining of less than half of the tumor cells were at equal or lesser intensity compared to the controls. Strong diffuse staining implied positive staining of more than half of the tumor cells at equal or greater intensity compared to the controls (Figures 1–5). The presence of a correlation was investigated between these IHC staining scores and WHO grade, recurrence, and brain invasion.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum values, frequency, and ratio values were used. To determine correlations between IHC staining and WHO grade, recurrence, and brain invasion, the chi-squared test was used in the analysis of qualitative independent data, and the Fischer test was used when the chi-squared test conditions were not met. SPSS vn.27.0 software was used in the analysis. Statistical significance was considered as $P<0.05$.

Figure 1: A: CD147 staining , score 1 (grade 1 meningioma) . B: CD147 staining, score 2 (atypical meningioma with brain invasion). C: CD147 staining, score 2 (grade3 meningioma)

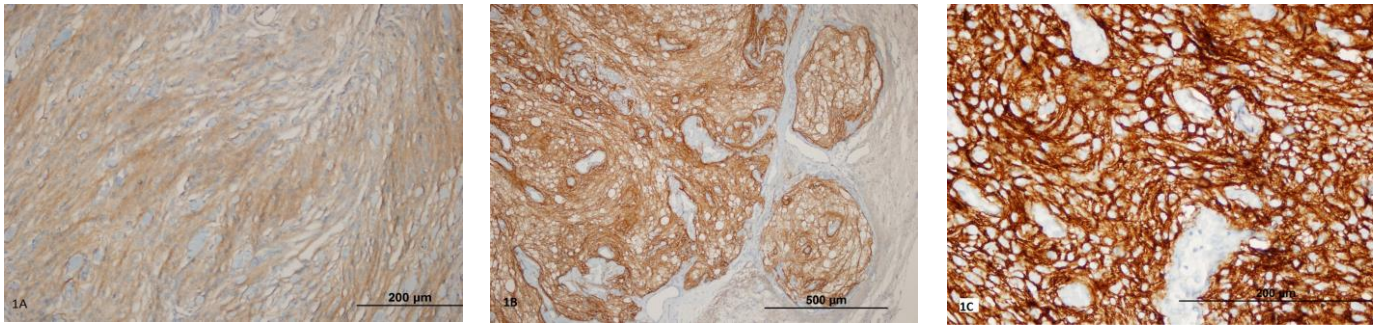


Figure 2: A: MMP2 staining, score 1, (atypical meningioma). B: MMP2 staining, score 2, (grade 1 meningioma)

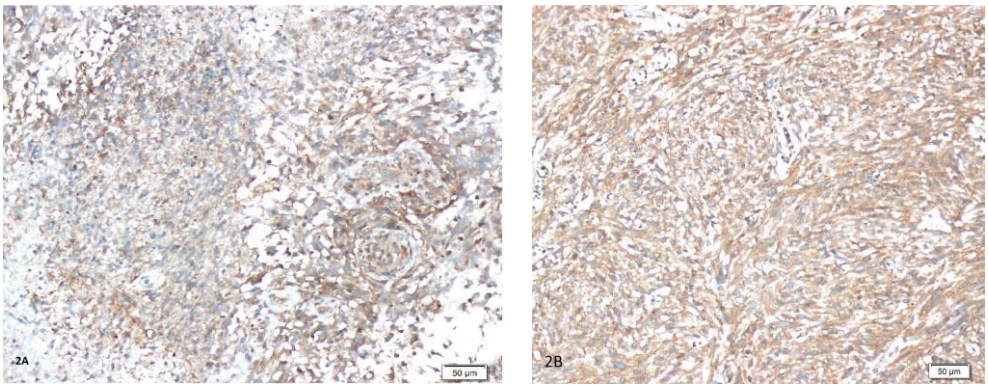


Figure 3: A: MMP9 staining, score 1, (atypical meningioma). B: MMP9 staining, score 2, (grade 1 meningioma).

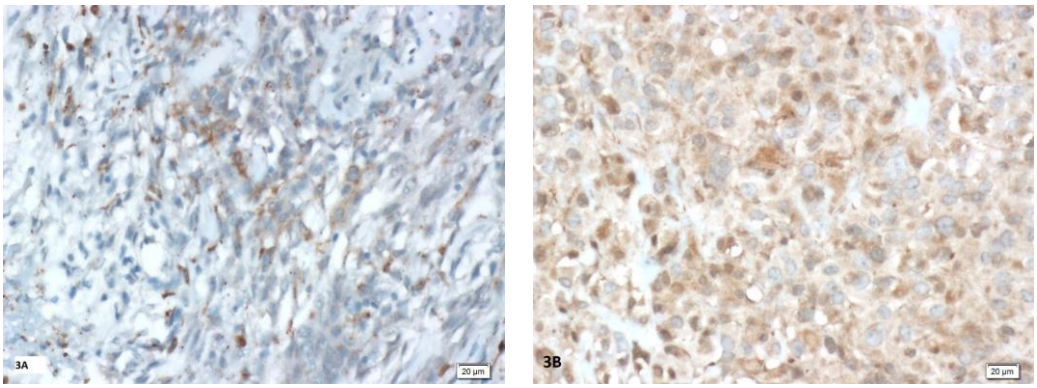


Figure 4: Galectin-3 (GAL3) staining, score 1 (anaplastic meningioma). B: GAL3 staining, score 2, (atypical meningioma).

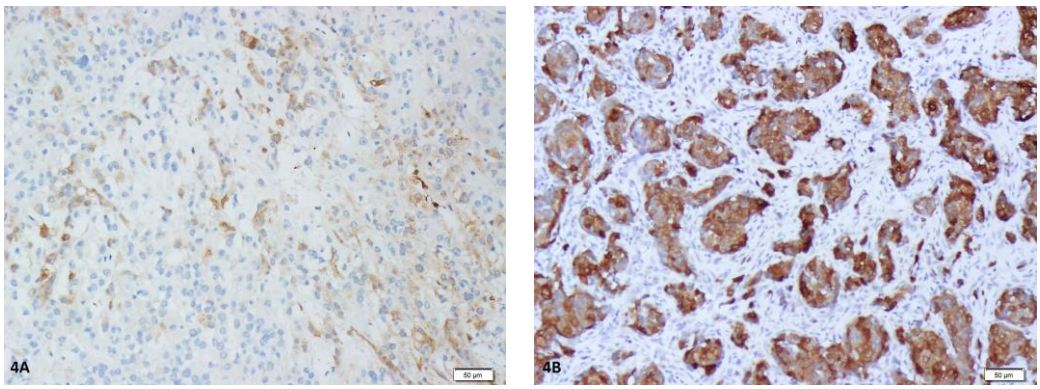
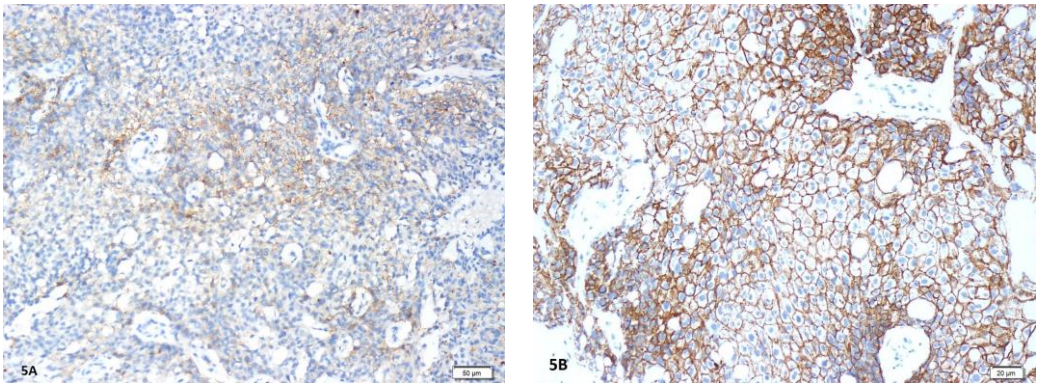


Figure 5: A: ECAD staining, score 1, anaplastic meningioma, B: ECAD staining, score 2, atypical meningioma.



Results

Of all the cases identified through the database searches, 231 cases met the study criteria. These 231 patients consisted 168 females and 63 males with a female/male ratio of 2.67. The mean and median age at diagnosis were similar at 57 years with a standard deviation of 14.4 years (range, 13–92 years). The histological review identified 198 Grade 1 tumors (85.3%), 28 Grade 2 tumors (12.6%), and five grade 3 tumors (2.2%). The distribution of the tumor grades was consistent with the previous reported series. Among the histological types, two chordoid (grade 2) and three rhabdoid (grade 3) variants were found. The majority of grade 1 tumors were of the fibrous (26%), meningothelial (25.5%), and transitional (23.4%) types. Brain parenchymal invasion was determined in 19 (8.2%) tumors. Tumors with brain parenchymal invasion were grade 2 (18 cases) or grade 3 (five cases). Recurrence information was available for 188 patients, and only 18 tumors recurred during the follow-up period (Table 1). As the number of grade 3 cases was insufficient, grades 2 and 3 were evaluated as a single group to obtain the most accurate results in the analysis of the statistical results of the IHC study. According to the results of the statistical analyses, a correlation between CD147 and WHO grade was found (P=0.009). No correlation was found between the other markers and clinical parameters (Table 2). Consistent with the literature, the rate of recurrence and brain invasion was higher in the group with grades 2 and 3 than in the grade 1 group.

Table 1: Clinical parameters of the patients included in the study.

		Min–Max	Median	Mean(SD)	%
Age (years)		13.0 - 92.0	57.0	57.0(14.4)	
TM Size (mm)		0.0 - 87.0	5.0	17.7(20.2)	
Follow Up (days)		3.0 - 3899.0	64.0	334.4(553.0)	
Gender	Female			168	72.7%
	Male			63	27.3%
WHO	Grade 1			198	85.7%
	Grade 2			28	12.1%
	Grade 3			5	2.2%
Recurrence	(-)			170	73.6%
	(+)			18	7.8%
	NA			43	18.6%
Brain invasion	(-)			212	91.8%
	(+)			19	8.2%

Table 2: Immunohistochemical scoring and statistical results

		Grade 1		Grade 2/3		*P*-value
		n	%	n	%	
CD147	No staining	54	28.3%	2	6.5%	0.009 X^2
	Weak staining	90	47.1%	15	48.4%	
	Similar or stronger staining compared to control	47	24.6%	14	45.2%	
MMP2	No staining	36	18.6%	5	15.6%	0.690 X^2
	Weak staining	86	44.3%	21	65.6%	
	Similar or stronger staining compared to control	72	37.1%	6	18.8%	
MMP9	No staining	99	50.3%	10	32.3%	0.062 X^2
	Weak staining	90	45.7%	20	64.5%	
	Similar or stronger staining compared to control	8	4.1%	1	3.2%	
Galectin	No staining	44	22.6%	7	21.9%	0.931 X^2
	Weak staining	50	25.6%	14	43.8%	
	Similar or stronger staining compared to control	101	51.8%	11	34.4%	
E-Cadherin	No staining	93	48.2%	10	32.3%	0.099 X^2
	Weak staining	70	36.3%	15	48.4%	
	Similar or stronger staining compared to control	30	15.5%	6	19.4%	

Discussion

The results of this study demonstrate that CD147 appears to be positively correlated with WHO grade in meningiomas. CD147 is a type I transmembrane glycoprotein, which belongs to the immunoglobulin superfamily and is expressed in the cell membrane in different hematopoietic, epithelial, and endothelial cell types [17,18]. Normal epithelial and fetal tissues have been shown to have low CD147 expression based on IHC analysis. However, CD147 is over-expressed in various tumors, including malignant melanoma, liver , ovarian, and lung cancers [18–20]. Recent studies have reported that CD147 plays a part in tumor proliferation, apoptosis, invasion, metastasis, multi-drug resistance, and glycolysis via the action of some molecules, such as MMPs and Caveolin [19,21]. Evidence that CD147 is overexpressed in cancers, consistent with its capability to induce MMP synthesis, suggests that this molecule acts as a key regulator of oncogenesis and is associated with one or more signaling pathways. CD147 was also identified as a poor prognostic factor in many cancers, including glioblastomas [16,20,22]. Furthermore, more recent research suggests that CD147 modulates antitumor CD8+ T-cell responses to facilitate tumor immune escape and could be a potential target for cancer immunotherapy [23].

Previous studies have suggested that MMPs have prognostic significance in meningiomas. In the current study, although no correlation was determined between MMPs and WHO grade, a strong positive correlation was determined between MMP2 and 9 expression (P<0.001), and similar strong correlations between GAL3 and MMP9 expression (P=0.001), CD147 and ECAD, MMP2 and GAL3, and between CD147 and GAL3 were found. It is possible that these molecules, which correlated with each other, are functionally interactive. Nevertheless, a direct correlation between WHO grade and matrix modifier protein expression is not easily demonstrable, and a single stain will hardly be of practical use in validating WHO grade in meningiomas. It is possible that when these molecules correlate with each other, they interact functionally.

Limited research in literature on CD147 expression in meningiomas has been published. Tsai et al. reported that “high grade brain tumors overexpressing CD147 and CD147 are positively correlated with WHO grades in human astrocytomas and meningiomas, suggesting that CD147 may be a therapeutic target in brain tumors” [22]. The current study outcome was consistent with the findings of Tsai et al. [22].

Limitations

In our study, the number of grade 3 meningiomas was low, and the clinical follow-up time was not long enough for a Kaplan–Meier survival analysis to be constructed.

Conclusion

In this study, CD147 expression based on IHC was found to be higher in high-grade meningiomas. According to the results, CD147 may be a prognostic marker and contribute to the distinguish of Grades 1 and 2 meningiomas, especially in cases with diagnostic difficulties, and more importantly, it may be a target for meningioma treatment. The need for further studies to support these findings exists.

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Research article

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The effect of minimal and high flow anesthesia on optic nerve sheath diameter in laparotomic gynecological surgery

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Ethics Committee Approval
The study was approved by University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital ethics committee (2011-KAEK-25 2018/11-06), each patient written informed consent was obtained from all patients. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Optic nerve sheath diameter (ONSD) is a surrogate parameter for intracranial pressure. This study evaluated the effect of anesthetics on ONSD in women undergoing surgery. We aimed to measure the effect of minimal and high flow anesthesia techniques on expiratory/inspiratory oxygen and carbon dioxide fraction values, hemodynamic parameters, and the optic nerve sheath diameter by ultrasonography in open gynecological surgeries.

Methods: In the present prospective cohort study, 80 patients who planned laparotomic gynecological surgery were divided into two groups: a high flow of 2 L/min and a minimum flow of 0.5 L/min. Anesthesia was maintained with 50% oxygen-50% air at 2 L/min and desflurane at 1.1 MAC in Group 1 (n=40) and 50% oxygen-50% air at 0.5 L/min and desflurane at 1.1 MAC in Group 2 (n=40). After 10–15 min, group 2 was administered minimal flow with 50–60% oxygen and 40–50% air at 0.5 L/min desflurane, and 10 min before the end of the surgery, the patients were switched to high flow with 50% oxygen-50% air at 2 L/min.

Results: Decreasing heart rates were higher in Group 2 (T0 P=0.001, T2 P=0.007, T3 P=0.035). There was a significant positive correlation between $EtCO_2$ at the 60^{th} min and optic nerve sheath diameter measurements in the minimal flow group (left ONSD r=0.440, P=0.004, right ONSD r=0.473, P=0.002). Although inspiratory oxygen values in Group 2 did not fall below 32%, it was lower than Group 1 except for the last measurement time.

Conclusion: Minimal flow anesthesia is as safe as high flow in terms of effects on optic nerve sheath diameter and oxygenation parameters in laparotomic gynecological surgery.

Keywords: minimal flow anesthesia, high flow anesthesia, ultrasonography, optic nerve sheath diameter, gynecological surgery

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Introduction

General anesthesia is characterized by reversible loss of consciousness, analgesia, amnesia, and muscle relaxation [1]. While the most preferred method in general anesthesia inhalation induction is the administration of the fresh gas flow of 4–6 L/min, there is gradually increasing interest in low fresh gas flow, which has multiple advantages [2]. Low-flow anesthesia is a technique that delivers at least half of the expiratory gas mixture back to the patient using rebreathing systems after carbon dioxide (CO_2) in the anesthesia circuit is absorbed [3,4]. The administration of low-flow anesthesia has advantages, including preventing environmental pollution, reducing costs, minimizing heat loss, and better preservation of tracheobronchial physiology [2]. Furthermore, measurement of hemodynamic parameters and pressure changes may occur in the intracranial space because of several disadvantages caused by improper use of low flow anesthesia, such as hypoxia, hypercarbia, over/low dose volatile agent, toxic gas accumulation. Thus, low fresh gas flow may be helpful in developing safer anesthesia methods.

The follow-up of ONSD (optic nerve sheath diameter) is often performed by USG, a fast, easy, and non-invasive method for diagnosing intracranial pressure changes. The optic nerve sheath is an anatomical continuation of the dura mater, and the subarachnoid space around the optic nerve constitutes continuity with the intracranial subarachnoid space. Therefore, any pressure increase in the intracranial compartment also affects the optic nerve, increasing the ONSD and leading to papillary edema. Although USG for intracranial pressure measurement does not entirely replace invasive intracranial pressure (ICP) measurement techniques, it has a high positivity value, especially in pressures over 20 mmHg.

In our study, we aimed to investigate the effects of minimal and high-flow anesthesia techniques on expiratory/inspiratory oxygen and carbon dioxide levels, hemodynamic parameters, and ONSD during laparotomic gynecological surgery.

Materials and methods

After the approval of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital ethics committee (2011-KAEK-25 2018/11-06) and written informed consent was obtained from all patients, 80 patients aged 18–65 years, with ASA I-II laparotomic gynecological surgery between October 2018 and April 2019, were included in the study.

The patients who were not included in the study were: patients with obstructive pulmonary disease, decompensated diabetes, a fasting period of more than 12 h, acute alcohol intoxication, chronic alcohol use, those who refused to participate in the study, who were not cooperative, could not speak the native language, had known eye disease (glaucoma, retinal detachment), had a previous history of eye surgery, had increased intracranial pressure findings (intracranial lesion, previous cerebrovascular diseases), had a body mass index of > 40 kg/m^2, and those who had ASA > III. Cases requiring high-flow anesthesia for various reasons, including a drop of FiO_2 below 30%, tidal volume drop, and CO_2 retention during the surgery, were excluded from the study.

Anesthesia induction was performed with 0.02 mg/kg midazolam iv, 1 mcg/kg fentanyl iv, 2 mg/kg propofol iv, and 0.6 mg/kg iv rocuronium in all patients in the study. All patients received mechanical ventilation with a tidal volume of 6 ml/kg, a respiratory rate of 12 breaths/min, and PEEP of 5 cmH_2O in the volume-controlled mode. A Drager Primus anesthesia machine (Dräger Medizintechnik, Lübeck, Germany) was used. Based on the closed-envelope technique, patients were randomly assigned to one of two groups of fresh gas flows, 0.5 L/min or 2 L/min high flow. For Group 1 (n=40), high-flow anesthesia was used with a mixture of 50% oxygen and 50% air at a rate of 2 L/min and desflurane at a rate of 1.1 MAC throughout the procedure.

Anesthesia maintenance was achieved by administering 50% oxygen - 50% air at 2 L/min and desflurane for 15-20 min to Group 2 (n=40). As soon as the MAC reached 1.1, it was switched to minimal flow with 50–60% oxygen, 40–50% air at 0.5 L/min, and desflurane was introduced. Approximately 10 min before the end of the surgery, the flow was switched to high flow with 50% oxygen and 50% air at a rate of 2 L/min.

Age, height, weight, ASA, systemic diseases, anesthesia, and surgical time of the patients were recorded. Heart rate (HR), mean blood pressure (MBP), peripheral oxygen saturation (SpO_2, end-tidal carbondioxyid ($EtCO_2$), PEEP, PEAK, MAC, FiO_2, and left-right ONSD measurements of the patients were recorded before and during the surgery at specified time points (T0: awake, T1: High fresh gas flow after induction at the 10th min, T2: Inhalation anesthesia at the 30th min, T3: Inhalation anesthesia at the 60th min, T4: Inhalation anesthesia at the 90th min, T5: Before extubating).

An experienced and the same anesthetist measured the diameter of the optic nerve sheath. A 12-MHz linear probe was used in conjunction with a GE Healthcare Logiq e series USG device. During the supine position, longitudinal and transverse axis images were obtained on both eyelids. A measurement was taken 3 mm behind the optic nerve head. The following complications were recorded during the surgery and recovery (respiratory distress, decreased oxygen levels, hypotension, hypertension, bradycardia, tachycardia, vomiting, and rhythm disorders).

Statistical analysis

Shapiro-Wilk was used to assess whether the data were normally distributed. The t-test was used for the normally distributed data and the Mann-Whitney U test for data not normally distributed in comparing the two groups. The correlations between variables were evaluated with Pearson correlation (r) and Spearman correlation (rho) coefficients. In the analysis of time-dependent measurements, percentage change from the first measurement was calculated (Percentage change=last measurement - first measurement / first measurement), and percent change values performed statistical comparisons between groups. Pearson Chi-square test, Fisher's exact test, and Fisher-Freeman-Halton test were used to analyze categorical data. Statistical data analysis was performed using SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) software program. The significance level was accepted as P <0.05.

Results

There was no statistically significant difference between the groups regarding age, weight, height, body mass index (BMI), ASA, and duration of anesthesia (Table 1). Bradycardia was observed in three patients in Group 1 and two in Group 2, and an allergic reaction was observed in one in Group 2.

Heart rate values were higher in Group 2 than in Group 1. When the 30th, 60th, 90th, and before extubation changes of HR measurements were compared, the decrease in the patients of Group 2 was higher than in those of Group 1 (Table 2) (T0 *P*=0.001, T2 *P*=0.007, T3 *P*=0.035).

Table 1: Comparison of demographic characteristics of groups

	Group 1 (n=40)			Group 2 (n=40)			*P*-value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Age (years)	48.00	32.00	66.00	48.00	26.00	65.00	0.747
Weight (kg)	67.00	51.00	98.00	70.00	50.00	120.00	0.435
Height (cm)	165.00	155.00	170.00	165.00	160.00	174.00	0.573
BMI (kg/m²)	24.60	19.40	35.80	25.30	19.50	44.00	0.637
Duration of surgery (min)	95.00	65.00	200.00	100.00	65.00	400.00	0.345

BMI: Body mass index, Mann-Whitney U test

Table 2: Comparison of hemodynamic data between groups [mean (SD)]

		T0	T1	T2	T3	T4	T5
HR	Group1	81 (15.38)	0.05 (0.2)	0.04 (0.2)	0.14 (0.2)	0.11 (0.1)	0.09 (0.2)
	Group2	93 (14.0)	0.02 (0.2)	0.18 (0.1)	0.22 (0.1)	0.20 (0.1)	0.14 (0.1)
	P-value	0.001**	0.223	0.007*	0.035*	0.078	0.309
MBP	Group 1	103 (12.5)	0.16 (0.1)	0.18 (0.1)	0.12 (0.1)	0.16 (0.1)	0.12 (0.1)
	Group 2	106 (16.9)	0.16 (0.1)	0.19 (0.1)	0.17 (0.1)	0.15 (0.2)	0.14 (0.1)
	P-value	0.396	0.320	0.683	0.218	0.857	0.508
SpO_2	Group 1	98 (2.0)	00 (0.02)	00 (0.02)	00 (0.02)	00 (0.01)	00 (0.01)
	Group 2	98 (2.5)	0.01 (0.02)	00 (0.03)	00 (0.03)	0.0 (0.01)	00 (0.02)
	P-value	0.772	0.399	0.451	0.264	0.935	0.216

*$P<0.05$, **$P<0.001$, Pearson Chi-squared test, HR: Heart rate, MBP: Mean arterial pressure, SpO2: Peripheral oxygen saturation, T1: High fresh gas flow after induction at the 10th minute, T2: Inhalation anesthesia at the 30th minute, T3: Inhalation anesthesia at the 60th minute, T4: Inhalation anesthesia at the 90th minute, T5: Before Extubation

No statistically significant difference was found when the time-dependent MBP and SpO2 values were compared between the two groups (Table 2). A significant weak negative correlation was found between the ONSD and MAC values at the 60th minute in Group 1 (r=-0.331, *P*=0.037) and the 10th minute in Group 2 (r=-0.342, *P*=0.031) (Table 3, Table 4).

A significant moderate positive correlation was observed between ONSD and $EtCO_2$ at the 60th minute in Group 2 (Table 4) (ONSD left r=0.440 *P*=0.004, ONSD right r=0.473, *P*=0.002).

The inspiratory oxygen values of Group 2 were lower than those of Group 1 except for the last measurement time point. Inspiratory oxygen values were measured above 32% in both groups (Tables 3 and 4).

Table 3: The correlation of ONSD left and ONSD right with EtCO2, FiO2, MAC, PEAK in patients in the high flow group

			T1	T2	T3	T4	T5
ONSD left	$EtCO_2$	r	0.080	0.201	-0.114	0.174	0.066
		P	0.622	0.213	0.482	0.428	0.688
	FiO_2	r	0.000	0.265	0.300	0.235	0.118
		P	0.999	0.098	0.060	0.281	0.468
	MAC	r	-0.005	-0.053	-0.266	-0.029	-0.373
		P	0.974	0.747	0.097	0.895	0.018*
	PEAK	r	-0.017	-0.052	-0.103	0.014	-0.053
		P	0.917	0.749	0.526	0.948	0.743
ONSD right	$EtCO_2$	r	-0.140	-0.037	-0.202	0.094	0.058
		P	0.389	0.823	0.212	0.671	0.720
	FiO_2	r	-0.173	-0.080	0.052	0.090	-0.067
		P	0.285	0.625	0.751	0.684	0.680
	MAC	r	0.106	0.107	-0.331	0.023	-0.308
		P	0.516	0.512	0.037*	0.916	0.053
	PEAK	r	-0.070	-0.107	-0.165	-0.375	-0.035
		P	0.666	0.512	0.309	0.078	0.830

*$P<0.05$, Pearson Chi-squared test, Fisher-Freeman-Halton test, ONSD: Optic nerve sheath diameter, EtCO2: End-tidal carbon dioxide, FiO2: The fraction of inspiratory oxygen, MAC: Minimal alveolar concentration, T1: High fresh gas flow after induction at the 10th minute, T2: Inhalation anesthesia at the 30th minute, T3: Inhalation anesthesia at the 60th minute, T4: Inhalation anesthesia at the 90th minute, T5: Before Extubation

Table 4: The correlation of ONSD left and ONSD right with EtCO2, FiO2, MAC, PEAK in patients in the minimal flow group

			T1	T2	T3	T4	T5
ONSD left	$EtCO_2$	r	-0.078	-0.018	0.440	0.347	0.121
		P	0.631	0.912	0.004*	0.123	0.458
	FiO_2	r	0.100	-0.140	0.010	0.094	0.114
		P	0.538	0.388	0.951	0.684	0.485
	MAC	r	-0.045	-0.272	-0.008	0.104	-0.009
		P	0.784	0.090	0.959	0.654	0.958
	PEAK	r	-0.242	0.034	-0.046	0.238	0.065
		P	0.133	0.834	0.776	0.300	0.692
ONSD right	$EtCO_2$	r	0.068	0.046	0.473	0.195	0.289
		P	0.679	0.778	0.002*	0.398	0.071
	FiO_2	r	0.043	0.047	-0.036	0.157	0.173
		P	0.793	0.772	0.827	0.496	0.286
	MAC	r	-0.342	-0.151	-0.138	-0.051	-0.301
		P	0.031*	0.353	0.397	0.827	0.059
	PEAK	r	-0.034	0.042	0.010	-0.067	-0.016
		P	0.834	0.799	0.953	0.774	0.924

*$P<0.05$, Pearson Chi-squared test Fisher-Freeman-Halton test, ONSD: Optic nerve sheath diameter, EtCO2: End-tidal carbon dioxide, FiO2: The fraction of inspiratory oxygen, MAC: Minimal alveolar concentration, T1: High fresh gas flow after induction at the 10th minute, T2: Inhalation anesthesia at the 30th minute, T3: Inhalation anesthesia at the 60th minute, T4: Inhalation anesthesia at the 90th minute, T5: Before extubation

Discussion

Advances in anesthesia devices and monitoring methods has made the administration of low-gas flow anesthesia popular. Apart from concerns such as adequate access to the inhalation agent of the patient and the availability of hemodynamic stability, the most important factor that prevents the low gas flow anesthesia technique from becoming routine practice is the possibility of hypoxia and hypercarbia occurring in the patient. Continuous monitoring of FiO_2, $EtCO_2$, anesthetic agent concentration in the system, the volume of expiratory gas, airway pressures, and hemodynamic parameters is mandatory to ensure a safe anesthesia administration [5]. In a study of prolonged laparoscopic surgery, no significant differences were found in hemodynamic variables and respiratory variables between minimal-flow and high-flow desflurane anesthesia [6].

Low-flow sevoflurane anesthesia, without using N_2O, has been reported to be a safe technique for hemodynamic parameters [7]. Another study reported that MBP and HR did not differ from baseline values and were stable in low-flow anesthesia with desflurane [8]. In our study, no hemodynamical difference was observed between the two groups. In some studies, from high flow to minimal flow with a fresh gas flow of 0.5 L/min, the airway pressure increased, and the minute volume decreased, so they readjusted the tidal volume to provide sufficient minute volume. As there was no difference in PEAK values between groups in our study, we did not need to change ventilation parameters.

The inspiratory O_2 concentration should be at least 30% to prevent hypoxemia and provide adequate O_2. It is reported that FiO_2 should be increased when minimal flow is administered [9]. Our study uses 50–60% O_2 with 40–50% air mixture. Inspiratory O_2 did not fall below 32% at measurement time points. Although inspiratory and expiratory O_2 concentrations were decreased in both groups, they never fell to FiO_2 values that could clinically cause hypoxia. There was no significant decrease in SpO_2 in the minimal flow group where FiO_2 was lower.

In one of the studies, FiO_2 concentration was found to be lower in the minimal flow group during minimal and high flow desflurane anesthesia performed in laparoscopic surgeries [6].

In a study performed in laparoscopic cholecystectomies, EtCO2 and cerebral oximetry showed no difference in groups of

minimal and high-flow anesthesia [10]. In another study, there was no difference between low- and high-flow desflurane anesthesia in terms of $EtCO_2$, MAC, and hemodynamic parameters [11]. Our study used standardized mechanical ventilation mood, tidal volume at 6 ml/kg, and the respiratory rate at 12/min to keep $EtCO_2$ levels in the ideal range. In our patients, $EtCO_2$ ranged from 25 to 40 mmHg. There was no statistically significant difference in $EtCO_2$ measurements between the groups.

We detected no ONSD differences related to age, gender, and ethnicity, which has been reported in other studies [12]. In our study, no significant difference was found between the groups regarding demographic characteristics and left-right ONSDs. Also, the highest ONSD value recorded at the 60th mi. of the minimal flow group was 4.8 mm. A weak positive correlation was found between $EtCO_2$ and right-left ONSDs at the 60th min of the minimal flow group. Conditions such as hypoxia and hypercarbia, which may increase intracranial pressure, might increase the optic nerve sheath diameter [13,14]. It has been shown that ONSD measurement can be used as a non-invasive indirect indicator in determining the ICP [15,16].

Animal models indicate that the ONSD increases at approximately 0.0034 mm per 1 mm Hg increase in ICP. An experimental study on pigs found a linear correlation between ONSD and increased ICP [17]. In a study about the sensitivity and specificity of ONSD compared with CT results, they were 100% and 95%, respectively [18]. A similar study stated that USG of ONSD could be useful in detecting ICP after severe brain injury in intensive care patients [19].

The absence of follow-up on the development of cognitive dysfunction during the postoperative period and the lack of cerebral oximeter measurement limited our study. Thus, we could have an idea about the oxygenation of the cerebral area only in cases where minimal flow anesthesia was applied.

Limitations

There were two major limitations to this study. The first is that the ONSD was monitored for 90 min after pneumoperitoneum was induced, and the patient was placed in a Trendelenburg position. Due to the interrupted pneumoperitoneum caused by the uterus removal, the ONSD could not be measured afterward. Observing trends in ONSD changes has been assumed to be feasible using 40 min of ONSD distension, which is instantaneous and useful for determining whether acute changes have occurred. In addition, the sample size was insufficient to conduct additional analysis, including an area under the curve analysis of the ONSD. A larger randomized study would be necessary.

Conclusion

Here we report that minimal-flow anesthesia can be as safe as high-flow anesthesia using the ONSD measurement method by USG, which has been used in evaluating intracranial space in recent years. We believe that the prejudice against low-flow anesthesia can be reduced by demonstrating that minimal-flow anesthesia can be safely performed in specific surgery groups, as in our study.

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Methodological quality of randomized controlled trials of home-based rehabilitation in knee osteoarthritis: A cross-sectional survey

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Ethics Committee Approval
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: This study aimed to evaluate the methodological quality of randomized controlled trials (RCTs) that examine home-based rehabilitation (HBR) trials for knee osteoarthritis (KOA) using the Physiotherapy Evidence Database (PEDro) scale and the nine methodology-related items of the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement.

Methods: Three electronic databases were scanned from baseline to October 10, 2021. Two reviewers independently evaluated the articles according to the two inclusion criteria: (1) in individuals diagnosed with KOA, at least one group received home-based rehabilitation as a study intervention and (2) at least one group received a comparison intervention or no intervention. The methodological quality of the included studies (n=22) was assessed using the PEDro scale and nine items of the CONSORT 2010 statement.

Results: Among 1557 RCTs, 22 studies that fulfilled our criteria were included in the review. The mean PEDro scale score was 5.77 (1.54). This result reflects moderate methodological quality. Concealed allocation (6; 27.3%), blinding of subjects (4; 18.2%), and (0; 0.0%) of therapists associated with the methodological quality were not reported in most studies. An author's expertise in epidemiology and/or statistics was 0.78 points (95% confidence interval [CI] 0.11–1.44), the multicenter study 0.94 points (95% CI: 0.19–1.68), and a one-unit increase in the total score of the CONSORT statement led to an increase in methodological quality of 0.55 points (95% CI: 0.34–0.76).

Conclusion: The methodological quality of most RCTs examining HBR in KOA that we included in our systematic review was moderate. The adherence of journals and authors to CONSORT checklists in reporting of studies may lead to an improvement in the methodological quality of future published studies.

Keywords: knee osteoarthritis, remote rehabilitation, PEDro scale, CONSORT statement, quality of methodological

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Introduction

Osteoarthritis (OA) is a very common rheumatic disease in older adults and affects the hips and knees most frequently the weight-bearing joints [1]. The global burden of knee osteoarthritis (KOA) is increasing in most countries, and it is expected that this burden will continue to increase with the aging populations in most countries. Raising the awareness of the population and policymakers about the risk factors of KOA and the importance and benefits of its management and the provision of adequate health care to patients with OA is recommended to manage the future burden of this condition [2]. In addition, the effectiveness of exercise therapy in KOA patients is supported by strong evidence with reduced potential harms and beneficial effects on overall health compared to other KOA treatments (such as analgesia or surgery) [3,4]. In light of this evidence, the inclusion of exercise therapy among the primary treatments offered for all people with KOA will help reduce future burden and cost [5].

Exercise leads to a significantly reduction in pain and improvements in function, performance, and quality of life in people with KOA [6]. Both rehabilitation programs, whether clinical-based or home-based exercises, provide these benefits for people with KOA [7,8]. Home-based exercise programs have the advantages of being inexpensive and require little or no equipment compared to clinic-based exercise programs [9]. In addition to these advantages, the progression of coronavirus disease 2019 as an epidemic worldwide created difficulties in healthcare services and has brought home-based rehabilitation (HBR) to the forefront even more than in previous years [10].

However, whether practicing home or clinic-based exercises, an appropriate exercise protocol is required to maximize the benefits of these exercises [11]. While creating these exercise protocols, the results of evidence-based practices are used in addition to clinical experience [12]. Randomized controlled trials (RCTs) are the gold standard for evaluating the results of clinical trials and are also valuable in clinical decision making in physiotherapy. However, the lack of methodological quality in such RCTs can make their results misleading. The methodology and findings of the published report must be clear, complete, and transparent for a study to accurately evaluate the results and benefits to patients [13,14].

Today, home-based exercises are at the forefront of treatment in patients with KOA. RCTs results are important when prescribing these exercise programs within the framework of evidence-based practices. However, no studies have examined the quality of methodological of RCTs related to HBR in patients with KOA. This study aimed to evaluate the methodological quality based on the PEDro scale and the methodology-related items of the CONSORT 2010 statement of RCTs that were used to examine HBR trials for KOA.

Materials and methods

The Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA) statement was used to guide the reporting of this review [15].

Study selection

We included RCTs released in English before October 10, 2021. The inclusion criteria of our study consisted of several parameters: (1) the participants in the articles had been diagnosed with knee osteoarthritis regardless of the stage and did not undergo any previous surgery related to knee osteoarthritis (such as total knee arthroplasty), (2) received home-based rehabilitation in at least one group, and (3) received a comparison intervention in at least one group (such as inpatient/outpatient physical therapy and/or medical therapy) or (4) no intervention/placebo. In addition, RCTs were also excluded if the publications were only in abstract form or were incomplete.

Data sources and search strategy

The search was conducted in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science using a combination of keywords such as ((((random[Title/Abstract]) OR random* [Title/Abstract]) OR randomized[Title/Abstract])) AND ((home-based [Title/Abstract]) AND rehabilitation[Title/Abstract]) OR exercise[Title/Abstract])) AND English[lang]). The search results were screened using titles and abstracts. The reference lists of included trials and review articles on the topic of home-based exercise in KOA were also manually reviewed to identify any additional trials for inclusion.

Study process

All articles obtained in electronic databases with relevant keywords were downloaded to EndNote X7.7 software, and both authors independently excluded duplicate articles using this software. The scanning of the remaining articles then occurred again. Scanning was done first according to the title, then as abstract. When an article title related to the subject that we examined was seen, it was evaluated in terms of abstract suitability. If the relevance was not sufficiently understood in the abstract, a separate file was created to examine the full text. After the two authors independently conducted this search, the third author was consulted when any discrepancy in the selected articles was found. The reason for exclusion was noted for each study that was found unsuitable during screening and was not included in the study.

Data collection

We used 11 items on the PEDro scale to evaluate the methodological quality of the articles. The Physiotherapy Evidence Database (PEDro) is one of the most comprehensive databases indexing randomized controlled trials that examine physiotherapy interventions [16]. In addition, the trials in the database are graded on the PEDro scale according to their methodological quality with a total of 0 to 10 points without including the first item in the scoring [17]. PEDro makes it easy for physical therapists to access high-quality research. Thus, the PEDro database provides an important source of information that supports evidence-based clinical practice in physiotherapy [18].

Higher scores on the PEDro scale reflect increased methodological quality [19]. PEDro score of 9 to 10 points were accepted as “excellent”, 6 to 8 points “good”, 4 to 5 points “moderate”, and studies below 4 points are considered “poor” quality [20]. The PEDro scale was evaluated independently by two authors, and in case of inconsistency, the third author was

consulted and the problem was resolved through discussion. Items of the PEDro scale downloaded from the PEDro website are presented in table 1 [21].

Table 1: PEDro Scale

1. Eligibility criteria were specified;
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received);
3. Allocation was concealed;
4. The groups were similar at baseline regarding the most important prognostic indicators;
5. There was blinding of all subjects;
6. There was blinding of all therapists who administered the therapy;
7. There was blinding of all assessors who measured at least 1 key outcome;
8. Measures of at least 1 key outcome were obtained from >85% of the subjects initially allocated to groups;
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated, or where this was not the case, data for at least 1 key outcome were analyzed by intention to treat;
10. The results of between-group statistical comparisons are reported for at least 1 key outcome;
11. The study provides both point measures and measures of variability for at least 1 key outcome.

The Consolidated Standards of Reporting Trials (CONSORT) statement was created in 1996 to standardize the reporting of RCTs [14], and the most recently updated guide was published in 2010 [13]. The last version of the CONSORT Statement consists of a 25-item checklist and flowchart that includes examination of different aspects such as the design, analysis, and interpretation of RCTs [22]. The CONSORT statement aims to help researchers design trials and guide referees and editors in the evaluation of articles. Thus, it is predicted that the clarity and transparency of the published trials can possibly be increased [13,14,22].

Based on the methodology of a previous study, nine methodology-related items of the CONSORT statement were used alongside PEDro to assess the methodological quality of the articles included in our study. Both discussions between the authors and use of the method from a previous study were effective on which CONSORT statement items should be included in our study. The methodological quality of the articles eligible for the study was evaluated independently by both authors using these two scales. Discrepancies in scoring were resolved in consultation with the third author. The nine CONSORT items are presented in table 2 [23].

We examined the websites of the journals to check whether the articles were edited according to the CONSORT statement of the journal in which they were published. In addition, we examined whether the authors in all studies were affiliated with the epidemiology or statistics departments of different academic institutions. If any of the authors in the studies had a relationship with these sections, we coded it as yes, and if no such a relationship existed, we coded it as no.

We gathered the study characteristics of each RCT included in our study under several headings: (1) first author's name, (2) article title, (3) journal name, (4) journal impact factor, (5) number of authors, (6) sample size, (7) number of groups (two arms or more than two arms), (8) length of follow up, (9) funding source, and (10) number of primary results.

Table 2: Nine CONSORT Items

1. Identification as a randomized trial in the title (CONSORT item 1a): The authors must use the word “randomized” in the title. This helps to ensure that the trial report was properly indexed in databases and easily identifiable by readers. This criterion was rated as yes (coded as 1) or no (coded as 0).
2. Number of randomized participants (CONSORT item 4a): This item refers to the number of participants initially allocated to groups. Larger sample size increases the probability of the article as greater external validity and increases statistical precision. The number of randomized participants was extracted from the methods section. This was coded as 1 for the number of randomized participants specified and 0 if not specified.
3. How sample size was determined (CONSORT item 7a): Authors must have identified how the sample size was calculated, so that the trial report would have a high probability to detect a clinically important difference. Trials fulfilled this criterion if the authors stated that a sample size calculation was performed prospectively and were coded as 1. Retrospective calculations were not considered and were coded as 0 along with articles which did include a sample size calculation.
4. Locations where the data were collected (CONSORT item 4b): This information was important to judge the applicability and the generalizability of the trial results. Social, economic, cultural, or environmental aspects can affect the external validity. The country was extracted from the methods section, and in the absence of this information we assumed that the trial took place in the country of the first author of the trial. We collapsed the countries into regions (ie, Africa, Asia, Europe, North America, Oceania, South America, missing). In the case of multicenter trials, we recorded the number of centers involved. In the absence of this information, the trial was considered to be a single-center trial. Multicenter trials were coded as 1, and single-center trials were coded as 0.
5. Number of primary outcomes (CONSORT item 6a): Trials may have 1 primary outcomes. The other outcomes of interest are secondary outcomes. We used the following keywords (or variants of these) to determine if 1 primary outcomes were specified: primary outcomes, main outcomes, major outcomes, or end point. The number of primary outcomes was recorded. Articles which specified primary outcomes were coded as 1, whereas those which did not were coded as 0.
6. Statistical adjustment for multiple primary outcomes (CONSORT Item 12b): This adjustment is necessary to avoid a false-positive result (type 1 error). This information was extracted from the statistical analysis section, and the following key-words (or variants of these) were used: adjustment for primary outcomes, Bonferroni, Tukey, or Duncan. This criterion was rated as yes (coded as 1) or no (coded as 0).
7. Participant flow diagram (CONSORT item 13a): A diagram describing the number of participants in each treatment group, those who actually received the treatment, those who were excluded, and those who were analyzed for the primary outcomes should be presented. We did not consider flowcharts of the trial design. This criterion was rated as yes (coded as 1) or no (coded as 0).
8. Clinical trial registration (CONSORT item 23): The trial must have been registered in a public domain to avoid selection bias. We did not check if the registration was prospective or not. This information was solely based on the trial report. This criterion was rated yes (the trial was registered; coded as, 1) or no (if there was no explicit evidence of registration; coded as 0).
9. Funding sources (CONSORT item 25): Trials can receive various types of funding. Trials that received funding from scientific agencies are more likely to have better quality because they were peer reviewed prior to the inception of the trial. In contrast, trials funded by the private sector may have conflicts of interest and may have bias. This criterion was rated as yes (coded as 1) or no or not reported (both coded as 0).

Statistical analysis

Descriptive statistics of included studies, including number and percentage were defined for dichotomous data, and continuous variables were defined as the mean (standard deviation [SD]) when they fulfilled the conditions of normal distribution, and as the median with the interquartile range (IQR) when they did not.

Studies that fulfilled each item of the PEDro and CONSORT statement were assigned one point, and those that did not were assigned zero points. In addition, the median (IQR) calculation was performed for the categorical variables in the CONSORT statement.

To examine the relationship between reporting quality and study characteristics, we identified five factors based on reports of studies in the literature [23–26]. Next, our authors discussed which of the relevant factors better fits our hypothesis. Our discussion resulted in five factors, including RCT in the title (yes versus no), total score for the 9-item CONSORT statement (continuous variable), author's affiliation with an epidemiology and/or statistics department (yes versus no), multi-center study (yes versus no), and sample size (sample size ≤60 versus >60). Included were categorized according to the median of sample sizes.

Table 3: Characteristics of the 22 RCTs included in our study.

Article No	First Author	Journal Name	Year	Journal Impact Factor	Number of authors	Sample Size	Number of groups (2 arms and >2 arms)	Length of follow up (week)	Number of center (n)	Funding Source *	PEDro Score (0-10 point)	CONSORT Statement Score (0-9 point)
1	O'Reilly et al	Annals of the rheumatic diseases.	1999	16.102	3	191	2	24	2	1	7	7
2	Thomas et al.	BMJ	2002	30.223	6	786	6	104	3	1	7	8
3	Bruce et al.	BMC musculoskeletal disorders	2012	2.002	6	41	3	14	2	2	5	7
4	Tunay et al.	Acta Orthop Traumatol Turc	2010	1.121	3	60	2	6	1	4	5	3
5	Thomas et al.	Arthritis Care & Research	2005	4.056	6	786	6	104	3	1	6	6
6	Aoki et al.	Journal of Physical Therapy Science	2009	-	6	36	2	12	4	4	5	3
7	Rogers et al.	South African Journal of Sports Medicine.	2011	-	5	12	2	8	3	2	3	4
8	Rogers et al.	Journal of sports science & medicine	2012	1.806	4	44	4	8	3	2	5	6
9	Chaipinyo et al.	Australian Journal of Physiotherapy	2009	5.440	2	48	2	4	1	1	7	8
10	Brismee et al.	Clinical Rehabilitation	2007	2.599	10	41	2	18	1	1	6	7
11	Baker et al.	The Journal of rheumatology	2001	-	6	46	2	16	2	1	7	7
12	Bennell et al.	Arthritis Care & Research	2017	4.056	14	168	2	72	7	1	9	7
13	Bezalel et al.	Physiotherapy	2010	2.478	3	50	2	8	1	4	6	6
14	Gail et al.	Physical therapy	2005	3.140	9	134	2	8	3	4	8	7
15	McCarthy et al.	Rheumatology.	2004	5.606	6	214	2	52	1	1	6	7
16	Talbot et al.	Journal of the American Geriatrics Society	2003	4.180	4	34	2	24	1	1	4	6
17	Talbot et al.	The Journal of rheumatology.	2003	-	4	34	2	12	1	1	4	4
18	Çolak et al.	Rheumatology international.	2017	1.984	10	78	2	6	2	1	6	7
19	Bennell et al.	Osteoarthritis and Cartilage	2020	4.793	9	128	2	12	3	1	8	9
20	Oh, Seung et al.	Aging Clinical and Experimental Research.	2020	2.697	4	60	2	20	2	4	4	4
21	Evcik et al.	Rheumatology international.	2002	1.984	2	90	3	12	2	4	4	3
22	Kawasaki et al.	Journal of Orthopaedic Science.	2009	1.259	11	102	2	24	6	4	5	5

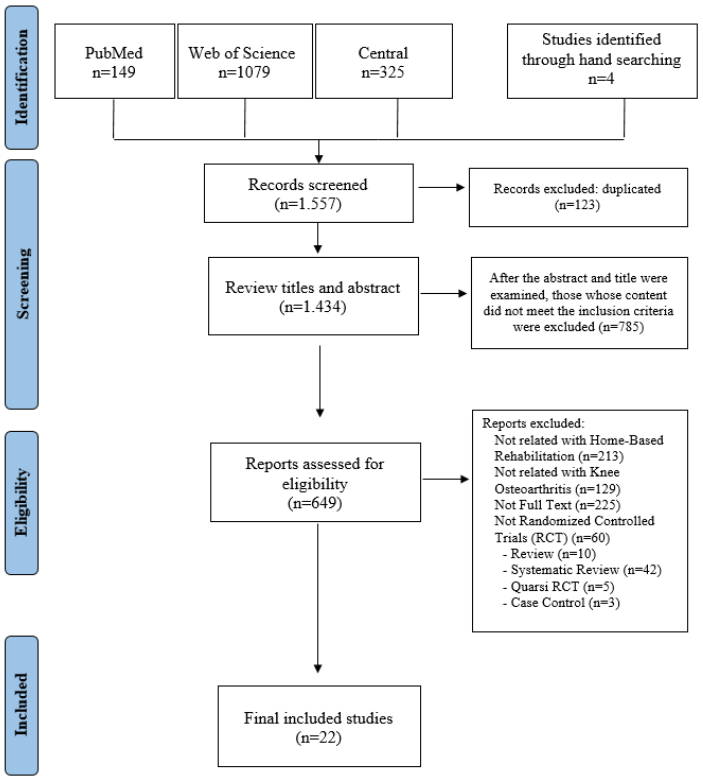
*** Funding Source:** Not-for-profit funding=1, For profit funding=2, Clearly stated, not funded=3, Not reported=4

We used univariable and multivariable linear regression analyses to examine the association of methodological quality with the pre-specified variables. We checked that the scores fulfilled the assumption of normality, collinearity, homogeneity of variance, normality of residuals, and variance inflation. To construct the regression model, we computed single predictive linear regression models between the dependent variable (total PEDro score) and each of the independent variables (identification as a randomized trial in the title, author's affiliation with a statistics and/or epidemiology department, number of centers, sample size, and total score for the 9-item CONSORT statement). We used the "Enter" analysis type in the regression analysis. We thought the model was complete when all variables reached a *P*-value of ≤0.05. Data were entered into an electronic database (Excel) and analyzed using statistical software (SPSS 22.0).

Results

According to our research strategy, the total number of studies obtained from databases was 1557. After title and abstract screening, 649 reports were found that were potentially available; upon reading the full texts, those who did not meet the inclusion criteria were excluded, and finally, 22 RCT reports were found to be eligible (Figure 1). Study characteristics are listed in table 3.

Figure 1: Flow diagram for searching and selection processes



These 22 RCTs were published between 1999 and 2020 among which 17 (77.3%) were two-arm trials, 12 (54.5%) were funded by not-for-profit funding agencies, and 13 (59.1%) were published in a journal that approved the CONSORT statement. Seventeen (77.3%) of the studies were graded based on the impact factor of the journal in which they were published, and the impact factor ranged between 1.121 and 30.223 (median 2.967). The sample sizes ranged from 12 to 786 (median: 60). The length of follow-up ranged from four to 104 weeks (median: 12 weeks). The median number of authors was six (IQR: 2–14) as shown in Table 4.

The overall mean total PEDro score was 5.77 (1.54). A small proportion of trials (six; 27.3%) reached a score of 6 to 8 points, indicating good quality [20]. Only one (4.5%) study achieved >9 points and was of very good quality [27].

Table 4: General characteristics of included Random Controlled Trials (RCTs)

Features of included RCTs	n=22, (%)
Sample size (Median [IQR])	
≤60 [a]	12 (54.5)
>60	10 (45.5)
Journal impact factor (Median [IQR])	
≤2.967 [a]	9 (40.9)
≥2.968	8 (36.4)
Journal has no impact factor	5 (22.7)
Number of arms	
2 arms	17 (77.3)
>2 arms	5 (22.7)
Length of follow up (Median [IQR])	
≤13 weeks [a]	11 (50.0)
>13 weeks	11 (50.0)
Sources of trial funding	
Not-for-profit funding	12 (54.5)
For profit funding	3 (13.6)
Clearly stated, not funded	0 (0.0)
Not reported	7 (31.8)
Published in a journal that endorses the CONSORT statement	
Yes	13 (59.1)
No	9 (40.9)
Number of authors (Median [IQR])	6 (2-14)

[a]: Median, IQR: interquartile range

Table 5 shows the percentage of trials that met each of the PEDro scale items. The following items of the PEDro scale were fulfilled in all studies, eligibility criteria in 22 (100.0%), statistical comparisons between groups in 22 (100.0%), and point measures and variability in 22 (100.0%). The least frequently fulfilled criteria were concealed allocation (6; 27.3%), blinding of subjects (4; 18.2%), and blinding of therapists (0; 0.0%). Details of the scoring of the included studies based on each item of the PEDro scale can be found in table 6.

According to the analysis of nine items of the CONSORT statement (table 7), only 12 trials (54.5%) included the definition as a randomized study in the title. Half of the trials showed (11; 50.0%) how sample size was determined. Most of the trials (15; 68.2%), conducted multicenter research. Regarding the region of the trial, the Asian continent had the highest trial rate (8; 36.4%), followed by North America (7; 31.8%), and Europe (5; 22.7%). More than half (15; 68.2%) of the trials identified a primary outcome (s). Only nine trials (40.9%) were statistically adjusted for primary results, and very few trials recorded research protocols (4; 18.2%).

Table 5: Percentage of articles meeting each Physiotherapy Evidence Database (PEDro) item (n=22)

PEDro Item	n (%)
1. Eligibility criteria and source of subjects	22 (100.0)
2. Random allocation	21 (95.5)
3. Concealed allocation	6 (27.3)
4. Baseline comparability	20 (90.9)
5. Subject blinding	4 (18.2)
6. Therapist blinding	0 (0.0)
7. Assessor blinding	10 (45.5)
8. >85% follow-up	11 (50.0)
9. Intention-to-treat analysis	10 (45.5)
10. Between-group comparisons	22 (100.0)
11. Point measures and variability	22 (100.0)
Total PEDro scale score mean (SD)	5.77 (1.54)

SD: Standard deviation

Table 7: Characteristics of articles according to the CONSORT statement items

Item	n (%)	Median (IQR)
Identification as a randomized trial in the title	12 (54.5)	
Number of randomized participants		
Reported	22 (100.0)	
Sample size		60 (102)
How the sample size was determined reported	11 (50.0)	
Locations where the data were collected		
Multicenter trials	15 (68.2)	
Number of trial centers		2 (2)
Continent where trial was conducted		
Europe	5 (22.7)	
North America	7 (31.8)	
Asia	8 (36.4)	
Oceania	2 (9.1)	
South America	0 (0.0)	
Africa	0 (0.0)	
Missing	0 (0.0)	
Number of primary outcomes		
Primary outcome(s) identified	15 (68.2)	
Number of primary outcomes		1 (3)
Statistical adjustment for multiple primary outcomes	9 (40.9)	
Participant flow diagram	17 (77.3)	
Clinical trial registration	4 (18.2)	
Funding sources	15 (68.2)	

Median, IQR: interquartile range

The final multivariate model is presented in table 8. The three independent variables were found to be associated with an increase in the total PEDro scale score. An author's expertise in epidemiology and/or statistics produced an increase in the score of 0.78 points (95% confidence interval [CI] 0.11-1.44), a multi-center study produced an increase in the score by 0.94 points (95% CI: 0.19–1.68), and each unit increase of the total score of the CONSORT statement produced an increase in the total PEDro score of 0.55 points (95% CI: 0.34–0.76). The multivariate model explains 78% of the total variance of the PEDro score (R^2: 0.780).

Table 8: Univariate and multivariate models of factors that may be associated with the PEDro total score

Variables	Univariable Analysis Coefficient (95% CI)	*P*-value	Multivariable analysis Coefficient (95% CI)	*P*-value
Identification as a randomized trial in the title				
yes vs no [ref]	1.87 (0.85–2.88)	<0.001	0.37 (–0.38–1.14)	0.332
Total score for the 9-item CONSORT statement	0.65 (0.41–0.90)	<0.001	0.55 (0.34–0.76)	<0.001
Author's affiliation to statistics or epidemiology department				
yes vs no [ref]	1.33 (0.15–2.52)	0.026	0.78 (0.11–1.44)	0.021
Center				
multicenter vs single center [ref]	0.92 (–0.37–2.21)	0.162	0.94 (0.19–1.68)	0.013
Sample size				
>60 vs ≤60 [ref]	1.33 (0.19–2.46)	0.021	0.26 (–0.45–0.98)	0.471

[ref]: reference level

Table 6: PEDro scores of included studies

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
O'Reilly et al. (1999) [39]	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Thomas et al. (2002) [40]	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Bruce et al. (2012) [41]	Y	N	Y	N	N	Y	N	N	Y	Y	5
Tunay et al. (2010) [42]	Y	N	Y	N	N	N	Y	N	Y	Y	5
Thomas et al. (2005) [43]	Y	N	N	Y	N	N	Y	Y	Y	Y	6
Aoki et al. (2009) [44]	Y	N	Y	N	N	Y	N	N	Y	Y	5
Rogers et al. (2011) [45]	Y	N	N	N	N	N	N	N	Y	Y	3
Rogers et al. (2012) [46]	Y	N	Y	Y	N	N	N	N	Y	Y	5
Chaipinyo et al. (2009) [47]	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Brismee et al. (2007) [48]	Y	N	Y	N	N	Y	N	N	Y	Y	6
Baker et al. (2001) [49]	Y	N	Y	Y	N	N	Y	Y	Y	Y	7
Bennell et al. (2017) [23]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Bezalel et al. (2010) [50]	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Deyle et al. (2005) [51]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
McCarthy et al. (2004) [52]	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Talbot et al. (2003) [53]	Y	N	Y	N	N	N	N	N	Y	Y	4
Talbot et al. (2003) [54]	Y	N	Y	N	N	N	N	N	Y	Y	4
Çolak et al. (2017) [55]	Y	Y	Y	N	N	N	N	Y	Y	Y	6
Bennell et al. (2020) [56]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Oh, Seung et al. (2020) [57]	Y	N	Y	N	N	N	N	N	Y	Y	4
Evcik et al. (2002) [58]	N	N	Y	N	N	N	Y	N	Y	Y	4
Kawasaki et al. (2009) [59]	Y	N	Y	N	N	N	N	Y	Y	Y	5

Discussion

This study is the first to investigate the quality of RCTs for HBR for KOA patients using the CONSORT statement 2010 and the PEDro scale. We included 22 studies that fulfilled our criteria. The overall methodological quality of these studies was suboptimal. Associated factors of higher PEDro scale score included the total CONSORT statement score, an author's statistical and/or epidemiological expertise, and/or multi-center execution of the study.

The methodological quality of RCTs in our study was moderate [20]. The total PEDro score of the previous study examining the quality of RCTs related to musculoskeletal conditions was also similar to our results with a the mean score of 5.27 (1.63) [23]. In addition, in another study of methodological quality in physiotherapy subdisciplines, the mean total PEDro score of studies in the musculoskeletal discipline was 5.08 (1.72) and was also consistent with our results [24].

In our review, we identified common methodological flaws regarding quality. Most of the studies we included did not report or underreported some features related to reporting methodological quality (concealed allocation, blinding, intention to treat, power analysis) according to CONSORT checklists. Articles with low methodological quality tend to exaggerate treatment effects and have a high risk of bias [28,29].

Concealed allocation associated with methodological quality was reported in only a few of the studies we investigated (six; 27.3%). In the previous quality reporting study, it was shown that the item of the least reported PEDro scale was concealed allocation [24,30]. Gonzalez et al [23] reported similar results (438; 31.2%). However, studies reporting this item more frequently have been published [25,26]. With these results, it was shown that studies examining HBR in KOA can both reduce the risk of bias and contribute to the methodological quality by reporting concealed allocation in compliance with CONSORT checklists.

Another item associated with the methodological quality is the intention to treatment (ITT) analysis, which describes the participation of individuals in the study in the analysis of their group even if they do not receive intervention. Thus, this parameter contributes to the external validity of the trials [31]. However, ITT was reported in almost half of the studies we included. ITT was reported more frequently in our study than in other studies [23,24,32,33]. However, this analysis was still inadequate in RCTs examining HBR in KOA. In order to ensure external validity of studies examining HBR in KOA, to increase their methodological quality, and to ensure the reliability of their results, ITT analyses following CONSORT checklists should be performed.

Also, blinding is associated with methodological quality. However, in the studies we included, blinding (subject, therapist, and assessors) was not at an optimal level. These results were similar to the results of the study reporting blinding

in the field of physiotherapy [34, 35]. Very few of the studies we reviewed reported blinding of subjects (four; 18.2%). This result was similar to Gonzalez et al. (161; 11.5%) [23]. In a study examining the quality of chiropractic RCTs, blinding of subjects was reported more frequently (16; 46.0%) [25]. Also, no blinding of the therapists was reported in any of the studies included in our study. This situation was similar to reports from studies examining blinding [23,34]. It should be emphasized that RCTs in the field of physiotherapy may be extremely difficult in terms of therapist blinding. In addition, blinding of the assessors can be applied to any study using simple procedures [24], but studies we included reported that this process was used in only about half. In the light of this information, even if it is difficult for therapists to be blinded in studies examining HBR for KOA, methodological quality can be improved by ensuring blinding of the assessors.

It is important to calculate the sample size correctly to obtain the correct results in RCTs. Excessively large sample selection may increase the cost; on the contrary, an excessively small sample size may lead to studies with low power [36]. However, the method by which the sample size was obtained was reported in only half of the studies we included. In previous studies, how the sample was found was not sufficiently reported [23,26,33,36]. On the contrary, more than half of the articles included in the study by Karpouzis et al. [25] provided information on the way in which the sample size was found. In addition, studies reporting that the quality increases as the sample size increases have been published [25,26]. However, for this purpose, we determined that sample size was not an associated factor with methodological quality in our study. Jia et al. [26]. also reached similar conclusions in their study. Thus, although we found that it was not related to methodological quality in the HBR studies in KOA, we think that performing power analyses and reporting information about the methods used to obtain these analyses were done may have an impact on the methodological quality so that the sample size in future studies in this area can be obtained at a sufficient level.

Based on our results, 12 RCTs (54.5%) included the designation as a randomized study in the title. Jia et al. [26]. reported that more than half of the RCTs in the title in studies that they examined presented results similar to our results. However, Gonzales et al. [23] showed that 626 (44.6%) expressions of RCT were less reported in titles. In the same study, they showed that inadequate reporting of RCT expression affects study quality. However, in our study, we observed that the inclusion of the RCT expression in the title did not affect methodological quality. One of the reasons that we could not find the expression of study design in the title as a determining factor associated with good methodological quality may be due to the higher frequency of expression of study type in the titles of the studies included in our study compared to the data examined in previous reviews.

Most of the studies we reviewed had received funding. A similar situation was reported in previous studies [23,26,33]. RCTs that receive funding are published in journals that have higher impact factors than RCTs that do not receive or specify this information, have a larger sample size, and better methodological quality [33,37]. The source of the funds was unclear in most studies. Future studies that examine HBR in KOA, if they are to receive funding, can improve methodological quality by using this funding for either the blinding of assessors or obtaining a larger sample size [24].

In our regression analysis, we observed a higher total CONSORT scale score yielded higher the methodological quality. RCTs published in journals requiring CONSORT compliance had higher scores on the PEDro scale [23,33]. However, the number of those who requested compliance with the CONSORT checklist from the journals published by the studies we included was 13 (59.1%). The use of reporting checklists (such as CONSORT statement) is mandatory in all journals, and journal referees and journal editors emphasize that the methodological quality can be improved by using the CONSORT statement during the review process [23,38]. If the CONSORT statement compliance of RCTs of HBR for KOA increases, the methodological quality may also increase. Another factor associated with the methodological quality of the studies we included was that the authors were experts in epidemiology and/or statistics. Authors with expertise in epidemiology and/or statistics are generally associated with higher quality studies. The results of our study also support this information, and we observed that methodologically higher quality studies are produced when one or more of the authors had statistical or epidemiological information. The last factor affecting the methodological quality in our study was that the studies were multi-center. Multi-center studies are of higher quality than single-center studies [26].

Our review has some limitations. Our review focused on three different databases, which are the most comprehensive databases of RCTs of physical therapy interventions [16]. However, we did not include the PEDro database, which is another comprehensive database in this field, and we only reviewed full-text articles published in English, so we acknowledge that we may have missed some RCTs for HBR in KOA. In addition, the choice of tools and methods used to assess the quality of RCTs will likely affect the rating of methodological quality. Therefore, in our study, we chose the PEDro scale, which was designed to assess the quality of RCTs in physical therapy interventions [17]. Our last limitation is that we did not include all 25 reporting items listed in the CONSORT checklist. However, the reason we did not include all items was that the same items evaluating the methodological quality on the PEDro scale were also included in the CONSORT statement. Therefore, based on an earlier study [23], we selected nine items from the CONSORT statement that did not match the PEDro scale items.

Conclusion

The reporting of most of the RCTs examining HBR in KOA, which we included in our study, was of low to medium quality. Among the items related to methodological quality, especially the blinding and concealed allocation items, most were insufficiently reported in many studies. The increase in the total CONSORT score, the author's expertise in statistics and/or epidemiology, and a multicenter study were associated with the methodological quality. Journals can improve the quality of studies by requiring adherence to CONSORT checklists in their

reporting so that readers, healthcare providers, and researchers can access more accurate, unbiased, and reliable results.

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Emergency and delayed microsurgical salvage of traumatic lower extremities

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Ethics Committee Approval
The study was approved by the Ege University Faculty of Medicine Local Ethics Committee of Clinical Studies (EGE-TAEK, https://aek-med.ege.edu.tr/index.php) on 09/17/2021, with approval number 21-9T/1.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The power of free flaps for lower extremity injury reconstruction is no longer a matter of debate; however, contrasting views remain regarding the timing of reconstruction. The mainstay article of Godina reported that reconstruction within the first three days after injury was more advantageous than surgery at later times, but different views about the best day for reconstruction have also been described in the literature. With developments in the field of microsurgery, plastic surgeons have become more experienced, shortened the times needed for surgery, and achieved flap success. We have also become more experienced with surgical times, and reconstruction on the day of injury has been performed as an emergency reconstruction (ER) procedure since 2018. However, despite the disadvantages of a delayed wait period, patients still experience delayed reconstruction (DR) due to their pre-operative conditions and dispatches from peripheral centers over delayed time periods. This study aimed to present our experiences with lower extremity reconstruction in emergency situations and after delayed periods with descriptions of technical tips for each situation.

Methods: Between 2018 and 2021, patients who underwent lower extremity reconstructions were examined as retrospective case-control study. Twenty-four patients (17 male and seven female) underwent lower extremity reconstructions with microsurgical free flap coverage. Patients' ages ranged from 6 to 75 years old. Ten patients underwent ERs (on the day of injury), and 14 patients underwent DRs. Twenty anterolateral thigh, two medial sural artery perforator, one latissimus dorsi, and one radial forearm flaps were chosen for reconstructions. Flaps were chosen for one-third of the distal lower extremity reconstructions (n=11) and Gustilo type 3B injuries (n=11), Gustilo type 3C injuries (n=1), and one-third for middle lower extremity soft tissue reconstructions (n=1). Infections, length of hospital stays, time spent during the reconstructive surgery, vascular complications, and additional debridement necessity counts were recorded and compared with previous statistical analyses.

Results: One venous thrombosis in the emergency group and three venous and one arterial thrombosis in the delayed group were reported. The patients were taken to the operating room immediately after which re-anastomoses were performed successfully, and all flaps survived. The hospital stay was between 4 and 60 days in the emergency group and 20 and 99 days in delayed group. Infections (P=0.03), vascular complications (P=0.04), and hospital stays (P=0.01) were statistically significantly lower in the emergency group than in the delayed group.

Conclusion: ER has many advantages, such as preventing time consuming surgeries and providing short hospital stays and low complication rates, over DR. However, DR is inevitable for some reasons, and despite its more complicated nature, meticulous flap follow-up and salvage procedures may provide the same flap success as found with ERs.

Keywords: delayed reconstruction, free flap, emergency reconstruction, lower extremity reconstruction

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Introduction

Traumatic lower extremity defects may be very challenging even for the experienced microsurgeons. Unlike head and neck, breast, or genital area reconstructions, which are usually elective and planned surgery, lower extremity injuries are generally performed by trauma surgeons in an emergency setting. However, these unexpected cases must be given the utmost consideration as they can result in major morbidities [1].

While the power of free flaps is no longer a matter of debate for reconstruction of lower extremity injuries, contrasting views remain regarding the timing of reconstruction [2]. Godina's 1986 study, in which the reconstructive time intervals were divided into the first three days, from three days up to three months, and more than three months, remains the mainstay in the literature. His study demonstrated that free flap surgery was more successful when performed in the first three days compared to the period of three days to three months since complications such as infection and flap failure were more frequent during the latter period [3]. Subsequent studies focused on investigating the correct timing for reconstruction, and many achieved more or less the same results as Godina [4,5]. However, Godina's 3-day cut-off was also modified in some studies [6].

One of the approaches is performing the reconstruction as rapidly as possible on the day of injury without waiting over the 3-day acute period as previously described by Godina . This newer method includes performing the reconstruction as an emergency protocol on the day/night of the injury. A large portion of lower extremity injuries tend to be admitted after working hours. Although it is more physiologically useful to cover exposed bone, tendon, or muscle with vital tissues as soon as possible, managing such complex surgeries during after-hours is not always possible [7,8]. Apart from the conditions of patients that dictate delayed surgery, some restrictive problems for emergency reconstruction, such as inadequacy of surgical equipment, operative staff fatigue, surgical experience, long operation times, and other factors, exist. Waiting for settlement of wound demarcation and the necessity of serial debridement is another advocated reason to wait [9].

In our previous algorithm, debridement and bone fixation were done as emergency procedures by orthopedic surgeons, and the patient was followed with a dressing as the first approach. The surgical plan for the patient should be determined as soon as possible. However, despite the advantages of acute reconstruction mentioned above, finding an early operation day for the patient is not always possible due to extensive surgical schedules and the length of the surgery to be performed. However, with developments in microsurgery, surgeons are becoming more experienced daily, and our center has also followed this evolution. An emergency microsurgery team was formed in 2018 with the aim of shortening operation times and increasing flap success. However, life-threatening conditions and patients that are referred late from peripheral centers are reserved for delayed surgery. This study aimed to present our experience of emergency and delayed microsurgical reconstructions with descriptions of technical tips for each situation.

Materials and methods

The Ege University Faculty of Medicine ethical committee approved this study with approval number 21-9T/1 on 09/17/2021. Patients who underwent surgery on for lower extremity soft tissue free flap reconstructions between 2018 and 2021 were retrospectively analyzed. Patients with lower extremity defects due to oncological surgery or trauma cases that were reconstructed without free flaps were excluded from the study. Twenty-four patients (17 male and seven female) were found to have free flap coverage for lower extremity injury. Twelve of 24 patients were referred to our emergency department on the day of trauma, and 12 were referred from other centers and were delayed. After detailed examination, two of twelve patients were not feasible candidates for emergency reconstruction because of subarachnoid hematoma in one case (Figure 1, 2) and drug abuse in the other, so they became delayed reconstruction (DR) candidates. The emergency reconstruction group (ER) consisted of 10 patients who underwent single-stage reconstruction: (1) debridement, (2) bone fixation if necessary, and (3) emergency free flap coverage by orthopedics and our team after-hours. Debridement was done until vital tissue was reached, and bleeding was accepted as the reference for stopping. Intramedullary nails, external fixators or plates, and screws were used as fixation tools. Free flap coverage started when orthopedic surgeons had finished their surgery, and the starting time of reconstructive surgery was recorded. Fourteen patients in the DR group underwent surgery based on a similar protocol that was done electively during working hours. All emergency and delayed patients underwent pre-operative computerized tomography angiography (CTA) for vascular assessment.

Anti-thrombotic agents were administered to all patients without early hematomas during the fourth post-operative hour. Frequent flap monitoring was carried out by experienced staff. The bone reconstruction stage was not included in the tables and statistical analyses in the study because the soft tissue had entirely healed. Patients were further analyzed for classical measures from similar studies: (1) surgery time, (2) infectious complications, (3) vascular complications/flap loss, (4) hospital stay, and (5) the necessity for an additional debridement [3,4].

Statistical analysis

The software SPSS v. 25.0 was used to conduct statistical analysis (IBM, Chicago, IL). Mann–Whitney U and *Chi-Square* tests were used to examine operative and post-operative values between two groups, and *P*-values <0.05 were accepted as statistically significant.

Figure 1: Patient No 1 in the delayed reconstruction (DR) group: A 6-year-old male patient was referred to our emergency department because of a motor vehicle accident. Emergency reconstruction (ER) was abandoned because of additional cranial damage. Image at the emergency department (A), After initial debridement and bone fixation, the wound was followed with dressing (B), Peri-operative image for soft tissue reconstruction, 17 days after injury (C), Harvested 18 x 11 cm anterolateral thigh (ALT) flap with single perforator (D), Reconstruction of exposed bone with ALT flap and granulation tissue with a split-thickness skin graft (E), Post-operative 19 months reconstruction (F). The patient was re-operated on the post-operative first day because of venous thrombosis. Salvage was done with excision of thrombotic vessel segment and venous re-anastomosis with a vein graft.

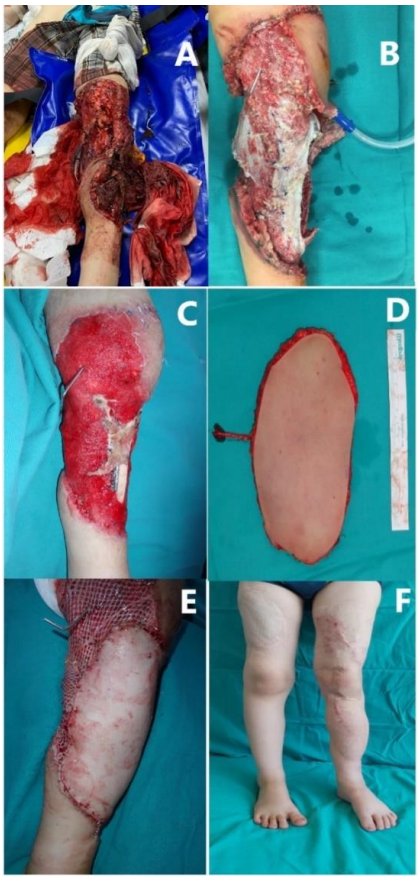
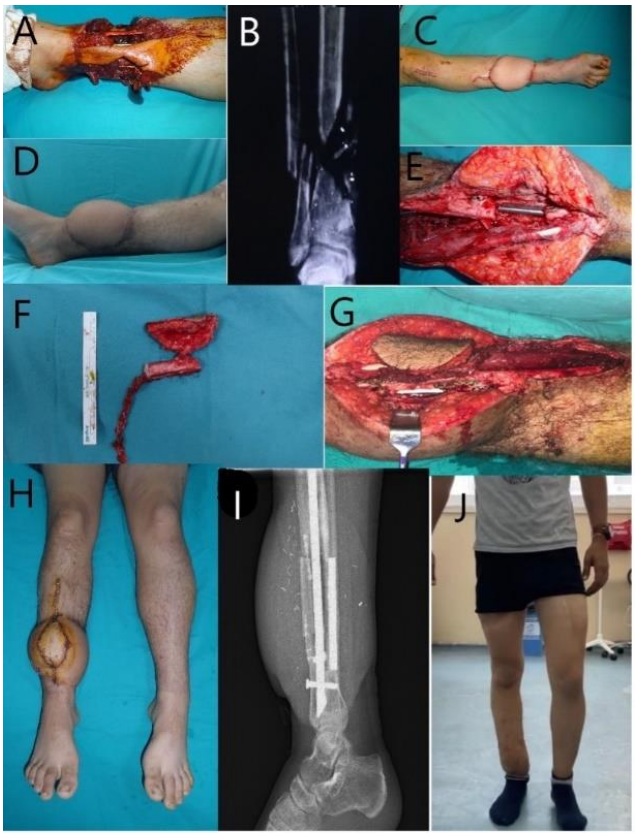


Figure 2: Patient No 4 in the ER gourd: A 22-years-old male patient was referred to our emergency department because of a gunshot injury. Bone fixation with intramedullary nailing (A), Pre-operative x-ray image of right distal tibia and fibula (B), Same sitting emergency soft tissue reconstruction with ALT flap after adequate sharp debridement, the pedicle of ALT was anastomosed to the anterior tibial artery (C), Post-operative 2 months after soft tissue reconstruction (D), Incision of completely healed ALT flap for bone reconstruction and defect of the tibia (E), Harvested free fibula flap with small skin paddle for flap monitoring(F), Inset of free fibula flap for bone reconstruction and supporting intramedullary nail, the pedicle of fibula flap was also anastomosed to the anterior tibial artery, proximal to first flap anastomosis line (G), Post-operative three weeks after bone reconstruction with ALT flap and skin paddle of fibula flap (H), X-Ray graph of bone reconstruction 3 weeks postoperatively (I), Post-operative two years after total reconstruction (J).



Results

Patient demographics are summarized in Table 1.

Infection

One patient in the ER (10%) and 5 patients in the DR (35.7%) groups had infections after surgery (Table 2). Internal plate and screws were removed, external fixation was applied to the patient in ER, and infection was handled with appropriate antibiotic protocols as was done for delayed infected patients. All infections were managed successfully except for one uncontrolled diabetes case in the DR. Despite a successful free flap survival on this patient; the extremity was amputated below the knee because of disseminated infection on the post-operative 25th day (P=0.03).

Vascular complications and flap loss

One patient (10%) in the ER group had venous thrombosis. In the DR group, three venous (21.4%) and one arterial thrombosis (7.1%) occurred after surgery. All vessels became patent with vein grafts, and all flaps were salvaged. The DR group had a higher complication rate (28.6%) than the ER group, and this difference was statistically significant (P=0.04).

Hospital stay

The minimum–maximum days of hospital stay ranged from 4 to 60 days, and the median value was 16 days in ER. The median value of the DR group was 40 days, and the minimum–maximum days ranged from 20 to 99 days. Hospital stays were longer with statistical significance in the DR group (P=0.01).

Reconstructive surgery time

Surgery time was recorded as the initial surgery. The time for flap salvages or additional debridement times were not recorded. The range of operative times was 2.5–4 h for the ER and 3.5–8 h for the DR groups. The median value was 3 h in the ER and 4.25 h in the DR groups. No statistical differences between groups were noted (P=0.16).

Additional debridement

One patient in the ER group (Figure 3) and two in the DR group had additional debridement. This parameter was not statistically significant between groups (P=0.33). All debridement were performed because of infections.

All results are summarized in Tables 2 and 3.

Table 1: Summary of patient demographics

Emergency Reconstruction	Sex	Age	Time of injury to free flap (day)	Comorbidity	Mechanism of injury	Type of Free Flap	Injury
Patient 1	Male	54	0	Tobacco+, HT	MVA	ALT	Distal 1/3 STD
Patient 2	Male	26	0	Tobacco +	MCA	ALT	Distal 1/3 STD
Patient 3	Male	24	0	Tobacco+	GSW	ALT	Distal 1/3 STD
Patient 4	Male	22	0	Tobacco +	GSW	ALT	Gustillo Type 3B
Patient 5	Male	17	0	None	MCA	ALT	Gustillo Type 3B
Patient 6	Male	26	0	Tobacco +	MVA	ALT	Gustillo Type 3B
Patient 7	Male	33	0	Tobacco +	MVA	ALT	Gustillo Type 3B
Patient 8	Female	50	0	HT	MVA	MSAP	Distal 1/3 STD
Patient 9	Male	36	0	Tobacco +	MCA	ALT	Gustillo Type 3B
Patient 10	Female	32	0	None	MCA	ALT	Distal 1/3 STD
Delayed Reconstruction							
Patient 1	Male	6	17	None	MVA	ALT	Gustillo Type 3B
Patient 2	Female	75	14	DM, HT, Tobacco +	MVA	ALT	Gustillo Type 3B
Patient 3	Male	64	60	DM, HT, BPH	MVA	ALT	Gustillo Type 3B
Patient 4	Female	30	32	None	GSW	MSAP	Gustillo Type 3B
Patient 5	Male	56	72	Tobacco+	MCA	ALT	Distal 1/3 STD
Patient 6	Male	10	33	None	MVA	ALT	Distal 1/3 STD
Patient 7	Male	42	34	Thrombocytosis	GSW	ALT	Distal 1/3 STD
Patient 8	Female	48	35	Tobacco +	MCA	ALT	Gustillo Type 3B
Patient 9	Male	38	21	Tobacco +	GSW	ALT	Distal 1/3 STD
Patient 10	Female	43	60	None	FFH	RFF	Distal 1/3 STD
Patient 11	Female	36	64	None	MVA	Latissimus Dorsi	Gustillo Type 3B
Patient 12	Male	54	33	None	MVA	ALT	Distal 1/3 STD
Patient 13	Male	23	39	None	MVA	ALT	Gustillo Type 3C
Patient 14	Male	34	24	None	MVA	ALT	Middle 1/3 STD

HT: Hypertension, MVA: Motor vehicle accident, MCA: motorcycle accident, GSW: gunshot wound, FFH: Fall from height, ALT: Anterolateral thigh flap, MSAP: Medial sural artery perforator flap, RFF: Radial forearm flap, STD: Soft tissue deficit, DM: Diabetes mellitus, BPH: Benign prostatic hyperplasia

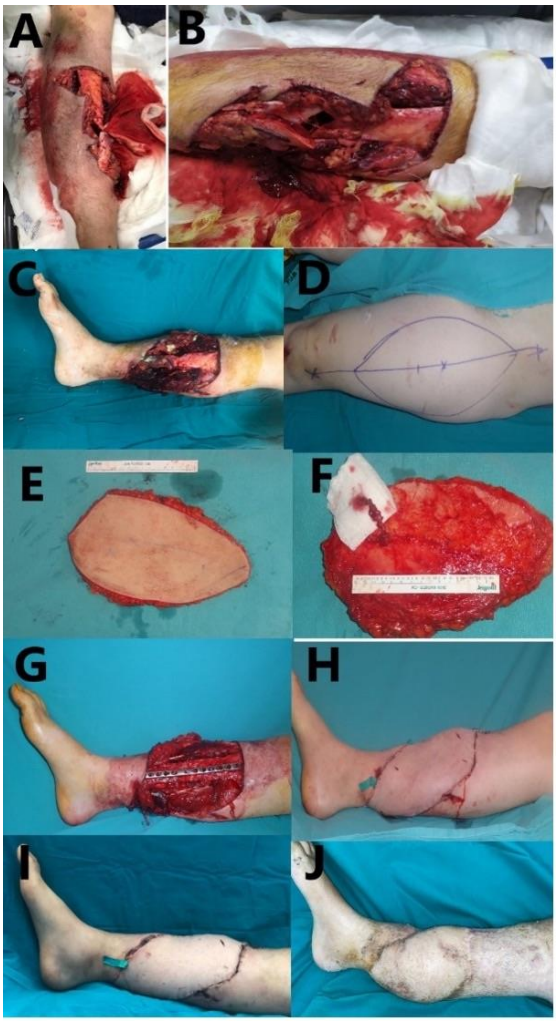
Table 2: Results of emergency and delayed group patients

Emergency Reconstruction	Length of Stay in Hospital (days)	Infection	Vascular Complication	Flap failure	Number of Additional Debridement	Time of Surgery for Reconstruction(hours)
Patient 1	13	None	None	None	0	2.5
Patient 2	4	None	None	None	0	3
Patient 3	13	None	Venous Re-anastomosis	None	0	3.5
Patient 4	20	None	None	None	0	3
Patient 5	60	Yes	None	None	1	2.5
Patient 6	29	None	None	None	0	3
Patient 7	15	None	None	None	0	3
Patient 8	17	None	None	None	0	3.5
Patient 9	12	None	None	None	0	4
Patient 10	18	None	None	None	0	3.5
Delayed Reconstruction						
Patient 1	35	Yes	Venous Re-anastomosis	None	0	4
Patient 2	40	Yes (Amputation)	None	None	0	4
Patient 3	40	None	Artery Re-anastomosis	None	0	3.5
Patient 4	30	None	None	None	0	4.5
Patient 5	99	Yes	Venous Re-anastomosis	None	1	8
Patient 6	20	None	None	None	0	3.5
Patient 7	42	None	None	None	0	4
Patient 8	62	Yes	None	None	1	4.5
Patient 9	48	None	None	None	0	5
Patient 10	26	None	None	None	0	4
Patient 11	34	None	None	None	0	6
Patient 12	51	None	None	None	0	5
Patient 13	53	Yes	None	None	0	4
Patient 14	40	None	Venous Re-anastomosis	None	0	5

Table 3: Statistical analysis between emergency and delayed groups

	Emergency Reconstruction	Delayed Reconstruction	*P*-value
Infection	Low	High	0.03 *
Vascular Complication	Low	High	0.04 *
Length of Stay in Hospital	Low	High	0.01 *
Time of Surgery for Reconstruction (h)	Low	High	0.16
Number of Additional Debridement	Low	High	0.33

Figure 3: Patient No 5 in the ER group: A 17-year-old male patient was referred to our emergency department because of a motorcycle accident. Images of the injury in the emergency department (A, B), Pre-operative preparation for early debridement, bone fixation, and soft tissue reconstruction in the operating room (C), Peri-operative planning of 25x15 cm ALT flap for soft tissue reconstruction (D), Harvested ALT flap with single perforator (E, F), Bone fixation with plate and screws (G), Post-operative image of soft tissue reconstruction (H), Re-operation for additional debridement and removing plate and screws because of infection three weeks after the initial surgery (I), Post-operative 20 months (J).



Discussion

One of the pioneering works about reconstructive time was published by Godina [3], who showed that the best results could be obtained during the first three days after injury, and the period ranging from 3 days to 3 months yielded more flap failures. Lee et al. [6] updated Godina's paradigm and extended the safe reconstructive cut-off day to 10 days. Haykal et al. [5] reviewed 43 articles, and the meta-analysis results showed that ER produced lower flap failure rates than DR. Roubaud et al. [10] examined 51 patients with reconstruction times <15 and >15 days, found no differences, and defined the subacute period as a safe reconstruction alternative. Steiert et al. [11] examined 33 lower and 10 upper extremity defects with pedicled and free flaps and found similar results between DRs and ERs.

Our center has been performing elective lower extremity reconstructions for many years. However, operations before 2018 were not included in the study that aimed to compare the emergency reconstructions and elective surgeries performed in the same period by the same surgical team. Although 24 patients applied or were referred to our center between 2018 and 2021, most patient underwent surgery from 2018 to 2019. We think the decrease in our patient count in 2020 and 2021 may have been caused by the coronavirus 2019 (COVID-19) pandemic since the ensuing curfews led to a reduction in the number of trauma patients with dressings who returned to the hospitals for follow-ups during this period due to fear of contracting COVID-19.

Many benefits of emergency reconstruction, both for patients and the workflow of the surgical unit, can be described. The time-consuming dressing changes, which occupy the medical personnel, are avoided. Operating room schedules for routine procedures are not affected as the cases are resolved after-hours [12]. Debridement and soft tissue reconstruction are applied in the same session, so the patient does not need to receive extra anesthesia. One of the limits for emergency reconstruction is the need for serial debridement as described in the literature [7,13]. Our study shows that serial debridement is not always necessary as emphasized by Singh et al. [12]. Sharp debridement of all devitalized tissue with meticulous visualization may avoid additional debridement.

With all benefits mentioned above, emergency reconstruction of lower extremity defects must become routine rather than a rare occurrence reserved for extreme cases. Patterson et al. emphasized that it would not be easy to perform this surgical procedure routinely, even in major centers, for various reasons [8]. Several measures are necessary to establish successful round-the-clock reconstruction of these cases in our experience.

It should be kept in mind that surgery will be performed under emergency rather than elective conditions. The evaluation, especially out of hours, may not be as detailed as the elective planned surgery. Therefore, it's beneficial to perform the surgery electively in the presence of the slightest situation that will put the surgery or the patient at risk. Concomitant life-threatening injury is one of the drawbacks [11,14]. Patient must be examined meticulously, and life-threatening injuries, and chronic or/and systemic diseases must be excluded, especially in young patients who abuse drugs or substances and may not mention this situation during the pre-operative evaluation.

The number of surgical teams, experience, and operation time are essential issues to consider in emergency conditions. It should be noted that the immediate reconstructive procedure for a lower extremity injury with intact circulation is not a real emergency. Even if there is no risk for the patient to receive general anesthesia, overlooked problems may be provoked by long operative times, so the time of surgery must be short as soon as possible. Therefore, while it is evident that surgical speed is not essential in surgical outcomes, speed also gains importance, especially in nighttime emergencies, for the above-mentioned reasons. Surgical procedures that take too long will be far from sustainable for the emergency reconstructions. We have two teams, one of whom is a backup for any situation of unavailability, and each team has two surgeons. Although it may be thought that larger surgical teams will increase surgical comfort, especially in elective cases, the surgical teams need to be used efficiently in emergency situations. Teams must be composed of a minimum count of staff who can complete the procedure efficiently.

Combining bone and excessive soft tissue defects deserves a more careful approach. Georgescu et al. used latissimus dorsi or serratus anterior muscles with ribs to

successfully reconstruct bone and soft tissue defects [15]. Although there are different options for repairing tibial defects, we think that one of the most suitable donors is the fibula, according to the reconstructive principle of "like for like." In cases in which the defect is too large to be closed with the skin paddle of the fibula in a single session out of hours, we find it more appropriate to complete soft tissue reconstruction first. The use of double-free flaps for both bone and soft tissue reconstruction at the same time is not applicable due to the above-mentioned conditions mentioned during the emergency period. One of the significant advantages of staged reconstruction in this type of injury is that it transforms a complex traumatic wound into an isolated bone defect covered with vital soft tissue. When complete soft tissue healing is achieved and since the flap will be revascularized from the neighboring tissues, it can be safely incised even disregarding the pedicle (Figure 2).

Godina [3] emphasized that fibrosis extends up to 10 cm from the trauma zone and reduces circulation by pressing on the veins, thus making the veins more susceptible to damage or tears. Although the reconstructive surgical time was not statistically different between the two groups and flap harvesting times were the same in our study, dissection of the recipient vessel, preparing the vessels for anastomosis, and the anastomosis times were long and difficult because of fibrosis and tissue edema. For the same reasons, vascular thrombosis and relevant complications can be seen at high rates in the DR group. For some cases, especially in the fibrotic zone, the veins appear to be hollowed out. When the vein is cut and inspected, no thrombus is found in the lumen; thus, it resembles an empty tube disconnected from circulation. Anastomosis should not be applied to such veins even if there are no suitable veins in the adjacent region, so a vein graft should be utilized to achieve a patent vein. Hill et al. [14] examined 60 free flaps and found thrombosis to be an essential factor for reconstructions after three days. In our study, vascular complications were higher in the D group. We think that the importance of the surgical time during the emergency period has been replaced by the importance of flap follow-up in the delayed period. Having medical personnel with sufficient experience in charge of flap monitoring is particularly important in late-term reconstructions.

We excluded controlled bleeding or leech therapy from our treatment algorithm years ago, especially after venous return problems. The salvage procedure is within our routine protocol in cases in which a problem with circulation is found. The first procedure used by our group is cutting the anastomosis, washing the lumen, and if possible, performing a thrombectomy. If a thrombectomy is impossible, it is essential to excise the thrombosed part of the vessels. However, in some cases, yellowish fibrin-like residues that remain attached to the vessel wall can be seen even after thrombectomy. These micro residues can be overlooked without meticulous microscopic examination, and the open lumen of the vessel may mislead the surgeon. So, vessel excision should be performed until it is certain that the lumen is clean. We note that after excision of the thrombotic vessel part, re-anastomosis should be performed without tension, and vein grafting should be performed even in case of slight hesitation about tension. One of the emergency group and four of the delayed group patients had vascular thrombosis. All flaps were salvaged after early exploration and vein graft application.

Most of the injuries that require free flaps are adjacent to the tibia. We consider it an essential advantage that the anterior tibial artery (ATA) is easy to access due to its proximity to the tibia, so it is the most frequently used as the recipient artery in our experience. For the same reason, ATA is known as the vascular structure most vulnerable to injury when compared with the peroneal or posterior tibial system in the literature [16]. Despite its frequent injury due to trauma and doubts about its choice as a recipient vessel by many surgeons, studies show that ATA can be used safely [17,18]. Our approach is to use it as the first choice. In cases in which the ATA is damaged, we prefer to anastomose to the appropriate segment by moving proximally. So, the structure of peroneal or posterior tibial vessels is preserved by using ATA as a recipient vessel whose contribution to the distal circulation has already been lost. However, especially in terms of middle lower extremity reconstructions, the effort to anastomose in a clean area by leaving the trauma zone requires passing a bulky anterior tibial muscle and reaching the deeply located ATA. Although various retractors used for this purpose provide direct access to the ATA during anastomosis, repositioning the thick anterior tibial muscle after the removal of the retractor can cause a loss of the length and pressure on the pedicle. Thus, it should be calculated in detail how far from the trauma zone an anastomosis will be done and how much pedicle length loss will occur due to deeply located recipient vessels, especially for mid-tibial region reconstructions.

Particular attention should be paid to the circulation in the extremities of patients whose initial condition is unknown and who are referred by an external center in the delayed period. Colen et al. [19] emphasized the benefits of CTA, and many centers use it to evaluate circulation or recipient vessels of the lower extremity. However, angiographic evaluation alone can be misleading due to artifacts in patients who underwent previous bone fixation. We find it important that even if no circulatory problem is detected angiographically or the presence of patent distal pulsations exists, the recipient vessels should be clamped peri-operatively for a while to confirm that no circulation problem in the distal part is present.

Although the efficacy of antithrombotic agents is controversial in terms of flap survival, we believe that the use of antithrombotic agents during late reconstruction is particularly beneficial. Lee et al. [20] examined 4984 cases in 12 articles, and their meta-analyses showed that the use of antithrombotic agents had no statistically different effect on flap survival. We believe that, rather than significantly impacting flap survival, anti-thrombotic agents buy the surgeon time for salvage surgery as these agents slow the settling of thrombosis into the vascular network.

In our opinion, when reconstructive microsurgeons encounter such patients whether in the emergency or delayed period, they should perform the reconstruction without waiting for the end or start of any period. Each period has unique and specific problems that need to be addressed. With the advances in microsurgery, reconstruction can be performed successfully either during the emergency or delayed period. At this point, we believe the main discussion should focus on unique challenges

and their solutions during different periods rather than choosing between them.

Conclusion

Emergency reconstruction has many advantages, such as preventing time-consuming procedures and providing short hospital stays and low complication rates. However, DR is inevitable for some reasons and despite its more complicated nature, meticulous flap follow-up and salvage procedures may provide the same flap success as found with emergency reconstructions.

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Reasons for requesting an interferon gamma release test from internal medicine and rheumatology clinics and evaluation of the results

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Ethics Committee Approval
The study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee dated 06.01.2023 and numbered 2023/31.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Tuberculosis is a disease involving many systems, such as the lung, gastrointestinal system, genitourinary system, etc. Detecting this disease in its latency significantly reduces the morbidity and mortality associated with tuberculosis. One of the tests used in latent TB screening is the interferon gamma release test. In rheumatology practices, it is routinely used to screen for latent tuberculosis infections before treatment with biological agents and Janus kinase (JAK) inhibitors, and it can also be used to exclude tuberculosis infection in clinical practice. In our study, we aimed to evaluate the reasons for requesting interferon gamma release tests and the results of this test in patients who requested it.
Methods: Patients admitted to internal medicine and rheumatology outpatient clinics were retrospectively screened within the retrospective cohort study. In total, 364 patients who requested interferon gamma release testing were included in the study. Nine patients with unclear test results were excluded. Laboratory results, demographic data, reasons for requesting the interferon gamma release test, and results were evaluated.
Results: The interferon gamma release test was requested by 355 patients. Of these, 266 patients (74.9%) asked for latent tuberculosis screening before treatment with biological agents and JAK inhibitors. This was followed by patients with peripheral lymphadenopathy-lung nodules, patients with unexplained elevated acute phase reactants, and patients with constitutional symptoms, respectively. Ten out of 107 patients (9.3%) had an active tuberculosis infection, while six out of ten patients (60%) had pulmonary tuberculosis, and four (40%) had extrapulmonary tuberculosis.
Conclusion: The most common reason for requesting the interferon gamma release test in internal medicine and rheumatology clinics was screening for latent tuberculosis before treatment with biologic agents and JAK inhibitors. In internal medicine, it has been observed that this test can also be requested by patients with constitutional symptoms, unexplained elevated acute phase reactants, and a preliminary diagnosis of tuberculosis in order to rule out or strengthen the preliminary diagnosis.

Keywords: interferon gamma release test, tuberculosis, biological agent

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Introduction

Tuberculosis (TB) is an infection caused by the Mycobacterium (M.) complex. This complex includes bacteria such as M. tuberculosis, M. bovis, M. caprae, M. africanum, etc., but it is M. tuberculosis that most commonly causes tuberculosis in humans [1,2]. When the human organism encounters M. tuberculosis, it can completely eliminate the bacterium before infection occurs, or it can become infected and develop into a primary or primary progressive disease. Another possibility is that an infection can develop against this bacterium, but most of the bacteria are eliminated and no clinical symptoms occur. This is called latent tuberculosis infection [3]. Latent infection may remain in the host for years without causing disease or may lead to active infection in the future. In low-incidence populations, tuberculosis is usually caused by activation of latent infection rather than primary progression [4]. When the disease becomes active, it can involve all systems, especially the lungs, and cause significant morbidity or death. Therefore, it is very important to recognize the disease in its latency to prevent mortality and morbidity [5].

Although there is currently no gold standard for diagnosing latent tuberculosis infection, the tuberculin skin test (TST) and interferon gamma release tests (IGST) are used for this purpose. These tests have their advantages and disadvantages [6]. Although there is no clear consensus on which one should be used in screening, the fact that the IGST provides an objective assessment and is more sensitive in populations where BCG vaccinations are common, puts it one step ahead. Positive results of these tests indicate exposure to TB bacilli but not active infection.

Latent TB screening is recommended for the high-risk group rather than the general population [7]. Anti-tumor necrosis factor (TNF) agents and Janus kinase inhibitors (JAK), which are widely used in internal medicine and rheumatology, may increase the risk of developing TB. This risk varies in proportion to the incidence of TB in the particular country or community [8]. Therefore, latent TB screening is routinely performed before anti-TNF treatment. Patients with a positive IGST or TST are given TB prophylaxis if they do not have an active TB infection. In addition to latent TB screening, IGST can also be requested to exclude or support the diagnosis of TB in patients with constitutional symptoms, such as fever, weight loss, night sweats, etc., as well as patients with unexplained acute phase reactant elevation, patients with peripheral-hilar-mediastinal lymphadenopathy (LAP), lung nodules, cavities or masses, especially in internal medicine practices.

In this study, we aimed to evaluate the reasons for requesting IGST and the results of this test in patients admitted to internal medicine and rheumatology polyclinics/clinics who requested IGST.

Materials and methods

Patients who applied to Afyonkarahisar Health Sciences University Faculty of Medicine Internal Medicine and rheumatology polyclinic/clinics from Jan. 10, 2020 to January 10, 2022 were contacted through the hospital electronic file system. Among these patients, those requiring IGST were identified. Patients under the age of 18 older than 85 with a history of active tuberculosis infection, chronic renal failure, a history of omcologic/hematologic malignancy, or immunodeficiency were excluded from the study.

Patients were divided into four groups according to their reasons for requesting IGST.

1) Patients with Constitutive Symptoms: Patients with complaints of fever, weight loss, night sweats, fatigue, etc. were included in this group.
2) Acute Phase Reactant Elevation: Patients with unexplained elevated sedimentation and C-reactive protein (CRP) were included in this group.
3) Those screened for TB before biologic agents and JAK inhibitors.
4) Those with peripheral-hilar-mediastinal LAP, nodules, cavities or masses in the lung.

Demographic data, laboratory values, and IGST results of all patients who requested an IGST and these patient groups were evaluated.

Ethics Committee

For this study, the decision of Afyonkarahisar Health Sciences University Faculty of Medicine Clinical Research Ethics Committee dated June 1, 2023 and numbered 2023/31 was approved.

Statistical Analysis

For statistical evaluation, the SPSS 26.0 (IBM Corp. 2019 IBM SPSS Statistics for Windows, version 26.0. Armonk, NY: IBM Corp.) program was used. Descriptive statistics were given as frequency, percentage, mean and standard deviation. The Kolmogorov-Smirnov test, which is a non-parametric test, was used for data with normal distribution. The Mann-Whitney U test was used for abnormally distributed data and the student's t test was used for normally distributed data for the differences between two continuous variable groups. Data with a *P*-value less than 0.05 were considered statistically significant.

Results

A total of 364 patients who requested an IGST were included in the study. Among these patients, nine were excluded from the study due to IGST uncertainty. Of the 355 patients, 143 (40.3%) were male and 212 (59.7%) were female. The youngest patient was 18 years old and the oldest was 83 years old. The mean age was 46.01 (15.20) years.

The laboratory results of the patients included in the study are shown in Table 1.

Among 355 patients, 107 (30.14%) tested positively on the IGST and 248 (69.85%) had negative results. Active TB was found in ten patients. Sixty percent of patients with active TB had pulmonary TB, while 40% had extrapulmonary TB. The most common reason for requesting IGST was for screening before the use of biological agents and JAK inhibitors in (266 patients; 74.9%). The reasons for requesting IGST, positivity and active/latent status are shown in Table 2.

Among the 80 patients with latent TB positivity before treatment with biologic agents and JAK inhibitors, 38 (47.5%) had previously used biologic therapy and JAK inhibitors. Of these 38 patients, 19 had previously completed INH prophylaxis and 51.42 (44.85) months had elapsed since then. Nineteen patients did not complete INH prophylaxis. Among these 19

patients, one patient on Adalimumab who did not receive INH prophylaxis developed active TB.

Table 1 : Laboratory results of patients for whom IGST was requested

	Minimum	Maximum	Mean	SD
WBC(mcL)	8.85	54600.00	9664.8137	2869.01703
HGB(g/dl)	8.1	18.8	13.337	1.9954
Platelet	21300	691000	299080.56	97012.377
AST(IU/L)	7.0	75.0	18.877	8.7891
ALT(IU/L)	3.0	120.0	19.858	14.2625
Urea (mg/dL)	4.7	143.6	29.736	13.0583
Creatinine (mg/dl)	0.31	78.00	1.1854	5.13457
Sedimentation (mm/h)	1	112	29.94	27.039
CRP (mg/dL)	0.10	294.92	19.9882	35.99428

SD: standard deviation, WBC: white blood cell count, HGB: hemoglobin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein

Table 2: Reasons for requesting IGST in the patients participating in the study and results thereof

	Number of IGST requests n (%)	IGST positivity n (%)	Active TB n (%)	Pulmonary TB n (%)	Extra-pulmonary TB n (%)
Patients with constitutional symptoms	14 (3.9)	3 (2.8)	2 (20)	1 (16.6)	1 (25)
Patients with Acute Phase Elevation	34 (9.6)	6 (5.6)	2 (20)	-	2 (50)
Before Biological Agents and JAK Inhibitors	266 (74.9)	80 (74.8)	3 (30)	3 (50)	-
Peripheral LAP, Patients with LAP-Nodules in the Lung	41 (11.5)	18 (16.8)	3 (30)	2 (33.3)	1 (25)
Total	355 (100)	107 (100)	10 (100)	6 (100)	4 (100)

A total of 42 patients (52.5%) were naive to biologic agents and JAK inhibitors. These patients were started on TB prophylaxis and no active infection has developed in their follow-up thus far. The biological agents, duration of the treatment and TB status of IGST positive patients who previously used biological agents and JAK inhibitors are given in Table 3.

While there was a statistically significant difference between WBC, sedimentation, CRP ($P<0.001$**)** among the patient groups who requested IGST (constitutional symptoms, acute phase reactant elevation, pre-biologic agent, peripheral LAP-lung nodule), there was no significant difference between other laboratory findings ($P=0.075$). In the post-hoc analysis, it was determined that this difference was due to the variance between the group for whom IGST was requested due to acute phase reactant elevation and the other groups. (Table 4).

Table 3: Biological agents used, duration and tbc status of IGST positive patients who previously used biologic agents and JAK inhibitor therapy

Biological agent	n (%)	Usage period Month	Completing prophylaxis	Active tb n (%)
Sertolizumab	7 (18.4)	23.28	1	2* (66.6%)
Tofasitinib	1 (2.6)	3	-	-
Tocilizumab	1 (2.6)	24	-	-
Anakinra	2 (5.3)	24	1	-
Adalimumab	11 (28.9)	60.63	8	1 **(33.3%)
Golimumab	5 (13.2)	36	2	-
Quadruple Treatment (Biological Agent+JAK inhibitor)	2 (5.3)	102	2	-
Binary Biologics	6 (15.8)	54.5	3	-
Infliximab	2 (5.3)	36	2	-
Etanercept	1 (2.6)	60	-	-
Total	38 (100)	42.30	19	3 (100)

* In a patient diagnosed with rheumatoid arthritis, IGST was negative before sertolizumab treatment, but IGST was found to be positive again in the 6th month of treatment due to constitutional symptoms and cough complaints, and cavitary lesion was detected on lung tomography. ARB was positive, cultures grew TB bacilli. ** This patient completed INH prophylaxis.

Table 4: Post-Hoc analysis between groups

	Std. Error	*P*-value.
Acute phase reactant elevation/Constitutional symptoms	32.587	<0.001
Acute phase reactant elevation/Pre-Biological agent	18.69	<0.001
Acute phase reactant elevation/Peripheral lap-lung nodule	23.803	0.087

Discussion

In our study, it was observed that the patient group in which latent TB screening was performed most frequently in internal medicine and rheumatology included those patients with rheumatologic diseases before biological agent treatment. In addition, IGST was requested by patients with constitutional symptoms, elevated acute phase reactants, peripheral LAP, and lung nodules, to obtain results quickly and to exclude TB or to support the diagnosis, since M. tuberculosis is a slow-growing bacterium (approximately six weeks to grow in culture). IGST results were evaluated in detail.

Anti-TNF alpha agents, one of the biologic DMARDs (disease modifying drugs), are widely used in rheumatology. TNF cytokine plays an important role in the immune response against mycobacteria by stimulating macrophages and increasing the release of various cytokines and chemokines [9]. It makes an important contribution to the killing of mycobacteria within the cell and to the maintenance of granulomas. Disruption of the TNF response with anti-TNF drugs disturbs granuloma formation and maintenance, leading to the proliferation of Mycobacterium tuberculosis [10,11]. As a matter of fact, with the increase in the use of these drugs, there has been a significant increase in TB infection. Long-term follow-up studies of individuals receiving treatment have shown an increased incidence of TB compared to the general population [12].

Therefore, latent TB screening is recommended by both national and international associations before starting this drug group [13,14]. Although there is no clear consensus as to whether TST or IGST should be used for latent TB screening or whether both should be used together, studies have shown that IGST is more effective [15]. Guozhong Zhou, et al. conducted a meta-analysis comparing the predictive values between IGST and TST, which indicated that IGST is two times more effective than TST in detecting latent TB infection and predicting progression to active disease [16]. Nazlıgül. et al. also found that IGST was a better method than TST as a latent TB screening method in 47 patients with chronic inflammatory arthritis [17]. In addition, in our clinical practice, IGST was used for latent TB screening before biological agent treatment in accordance with the literature.

In a study by Lee et al. [18], 342 patients underwent TST and IGST before biological agents, and the decision for TB prophylaxis was based on the results of IGST. IGST positivity in these patients was found to be approximately 30%. All patients with positive IGST results received TB prophylaxis. After a mean follow-up period of 41.7 months, five patients developed active TB. Of these patients, four were initially IGST negative, and one was initially IGST positive and developed active TB despite receiving TB prophylaxis. In our study, IGST was requested by 266 patients before biological agents, and positive results were found in 80 patients (30.14%). Active infection developed in three patients receiving biologic agent treatment, and one of these patients developed active disease after completing INH prophylaxis. The mean duration of biological agent use in patients with active TB was 35.73 months. The findings in the current study were similar to those in the literature.

In studies examining the data of patients using biological agents in countries such as France, England, and Spain, it was reported that TB infections developing after anti-TNF agents were mostly extrapulmonary. The same data showed

that patients using adalimumab and infliximab had a higher risk of developing TB than those using etanercept [12,19,20]. In our study, IGST positivity was higher in patients using adalimumab and infliximab than in patients using other biologic agents. Patients who developed active TB were those on adalimumab and sertolizumab. In our study, all of the active TB infections that developed due to the use of biological agents were pulmonary tuberculosis, unlike the literature. This may be explained by the low number of patients with active TB infection.

IGST positivity is not an indicator of whether the patient has an active infection. A positive test indicates whether the person has had previous exposure to TB bacilli. However, since it takes up to six weeks for TB bacilli to grow in cell culture, this test can sometimes be used to support clinical and radiologic diagnosis in patients with TB symptoms and to start treatment rapidly, or conversely, to exclude TB infection. In a study by Caliskan et al. [5], IGST was performed in 51 patients with suspected TB and positivity was observed in 12 patients (24%). Of these patients, four (33.3%) were found to have active TB infection. Similarly, in our study, IGST was requested from 89 patients with suspected TB, and positivity was observed in 27 patients (30%). Active TB was observed in seven (25.9%) of the positive patients.

The most common symptoms of patients with active TB infection include high fever, coughing, and night sweats. In addition, TB-specific nodules, cavitary lesions, and peripheral LAPs can be seen in the lung. Kurt et al. evaluated 38 patients with active TB infection and found constitutional symptoms, such as fever in 82%, night sweats in 48%, and anorexia in 20% of these patients. In addition, LAP was present in 57% of the patients [21]. Gülbay Eriş et al. [22] evaluated patients with active pulmonary TB and found that 35.9% had fever and 45% had night sweats. In our patient group, in accordance with the literature, TB was considered as a preliminary diagnosis in patients with constitutional symptoms, such as night sweats, anorexia, fever. Peripheral LAP and IGST were requested to support or rule out the diagnosis.

Limitation

The most important limitation of our study is that it is retrospective, and screening for tuberculosis was done only with the interferon gamma release test. There is a need for multi-center, prospective studies with large patient participation in this regard.

Conclusion

In summary, IGST is the most common internal medicine and rheumatology clinic screening used for latent TB infection prior to the use of biologic agents and JAK inhibitors. If active TB is not detected in positive cases, it is requested to prevent activation by giving prophylaxis. In the current study, it was observed that 38 patients with IGST positivity had previously used biological agents and JAK inhibitors for an average of 42.3 months. It was concluded that IGST positivity was seen more frequently in patients using adalimumab and certolizumab than in patients using other biologic agents and JAK inhibitors. In addition, especially in internal medicine, TB infection appears in patients with unexplained acute phase reactant elevation, in patients with constitutional symptoms and in patients with Lung nodules/hilar LAP. In patients with these symptoms, it was concluded that IGST was requested by the clinician to quickly rule out TB or to exclude its diagnosis, since TB bacillus is a bacterium whose growth is delayed.

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Investigation of sleep quality and musculoskeletal pain of university students during the pandemic period

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Ethics Committee Approval
The study was approved by Ankara Yıldırım Beyazıt University ethics committee (Date/no:08.12.2020/65).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The transition to distance education due to the coronavirus-19 restrictions changed the routines of university students, and physical activity and sleep status were affected due to increased computer screen use. Determining the factors affecting the sleep quality and musculoskeletal pain of university students during the pandemic period will guide the measures that can be taken to address these changes. The aim of this study was to investigate sleep quality and musculoskeletal pain of university students during the pandemic. Our research asked, "What are the factors affecting sleep quality during the pandemic period and does a difference between the musculoskeletal pain of those with good and bad sleep quality exist?"
Methods: University students receiving distance education were included in this cross-sectional study. Students' demographic characteristics, exercise habits, daily use of smart mobile devices were questioned via an online form. The Pittsburgh Sleep Quality Index was used to evaluate sleep quality, and the Cornell Musculoskeletal Discomfort Questionnaire was used to evaluate musculoskeletal pain. Sleep quality status based on regular exercise and daily mobile device usage time were compared. In addition, the musculoskeletal discomforts of the participants with good or bad sleep quality were compared.
Results: Two-hundred twenty-one university students were included in the study (187 female, 34 male). Sleep quality was better in those who exercised regularly (P=0.005). Subjective sleep quality and sleep latency scores were better for those who used smart mobile devices less than 5 h a day (P=0.002 and P=0.018, respectively). Those with good sleep quality had less musculoskeletal discomfort (P<0.001).
Conclusion: The findings of our study showed that increased physical inactivity and smart mobile device use during the distance education period negatively affect sleep quality. Since those with poor sleep quality have more musculoskeletal pain, we think that preventive measures, such as reducing screen time and inactivity, should be taken in distance education students to prevent health problems that may be associated with poor sleep status.

Keywords: sleep, exercise, screen time, pain, distance education

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Introduction

The coronavirus-19 (COVID-19) pandemic is a respiratory infection that first started in Wuhan, China in December 2019 [1]. It was declared a pandemic by the World Health Organization in March 2020, and many countries have taken precautions, such as social isolation and restriction to prevent the spread of the epidemic [2]. The process of distance education started in universities in Turkey in March 2020 [3]. During the distance education period, the routines of the students changed, and affected many conditions, such as physical activity, screen usage time, and sleep quality [4].

Sleep is a vital physiological event that is necessary for the continuity of body functions [5]. Sleep disorders are associated with many psychological and physical morbidities [6]. Good sleep quality also positively affects students' academic performances [7].

Pandemic restrictions have led to longer use of digital devices and changes in physical activity and sleep patterns [8]. Interrupting face-to-face education increases the risk of sleep disorders in students. This interruption can lead to deterioration of sleep quality and health problems that may be related to sleep [9]. On school days, while most students usually go to bed early and get up at a set time to go to school [10], it has been determined that university students go to bed later and wake up later and their sleep quality has decreased during the pandemic period [11–13].

It is known that physical activity during the day positively affects sleep at night [14]. Mahfouz et al. reported that physical activity was associated with good sleep quality in university students [15]. It has been stated that long-term use of smartphones negatively affects the sleep quality of students [16]. With the start of the distance education process during the pandemic period, the physical activity level of university students decreased while the duration of smart mobile device usage increased [17,18]. However, minimal attention has been given to how these changes affect sleep quality. If the effect of decreased physical activity and increased smart device usage time on sleep quality in the distance education process is understood, it can suggest an idea about what can be done to increase the sleep quality associated with academic success in students.

Sleep and musculoskeletal pain are interactive conditions. Pain can negatively affect sleep, and a sleepless night can cause pain to be felt more intensely the next day [19]. Approaches to improve sleep can also help reduce chronic pain [20]. Knowing the effect of sleep quality on the musculoskeletal system in distance education students is important in terms of showing the effect of sleep management on pain in the distance education process. We hypothesized that those with poor sleep quality might have more musculoskeletal pain. The aim of the study was to determine sleep quality status and musculoskeletal system pain of distance education students during the pandemic period, to examine the effects of long-term use of smart mobile devices and regular exercise habits on sleep quality, and to determine the effect of sleep quality on musculoskeletal pain.

Materials and methods

Participants

Volunteer students from 6 different universities in Turkey participated in this cross-sectional study. Ethics committee approval of the study was obtained from Ankara Yıldırım Beyazıt University ethics committee (Date/no: 08.12.2020/65), and the study was carried out in accordance with the rules of the Declaration of Helsinki. Inclusion criteria for the study were voluntary participation, participating in distance education, and being a university student. The exclusion criteria were non-volunteer and having had an illness/surgery that may have affected pain and sleep during the last six months. The study was carried out between February and April 2021. An online survey was prepared to evaluate sleep quality and musculoskeletal pain of the university students during distance education period. The online survey link was sent to students via e-mail or message. At the beginning of the online survey, an information about the purpose of the study was provided. All students marked an option stating that they voluntarily participated in the study before starting the survey.

Descriptive characteristics of students such as age and gender were recorded. Daily smart mobile device usage time and regular exercise habits were questioned. In previous studies, it has been reported that screen use time over 5 h has negative effects on health [21,22]. Therefore, to determine the effect of mobile device use on sleep quality, students were grouped as those with equal or less than 5 h of use and those with more than 5 h of use. Students were also asked whether they exercised at least 30 min per session, twice a week or more, and were considered to have regular exercise habits if answering "yes" [23]. The Cornell Musculoskeletal Discomfort Questionnaire (CMDQ) was used to assess musculoskeletal pain, and the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.

Instruments

The Turkish version of the CMDQ was used to evaluate musculoskeletal pain. CMDQ is a questionnaire that questions pain or discomfort felt in different body parts over the last week. It examines the frequency and severity of pain felt in twenty different body parts in the last week and its effect on work performance. Scoring for each body part is calculated by multiplying the frequency, severity, and work performance scores of the discomfort. The score for each body part ranges from 0 to 90. The total score is calculated by sum of the scores of all body parts. Higher scores indicate greater frequency and severity of pain and a greater negative impact on work performance [24].

PSQI Turkish version was used to evaluate sleep quality. This scale includes 24 items and seven subscales that evaluate sleep quality in the last four weeks. The last five items are answered by the person's roommate and these items are not included in the scoring. Subscales are subjective sleep quality (PSQI-1), sleep latency (PSQI-2), sleep duration (PSQI-3), sleep efficiency (PSQI-4), sleep disturbance (PSQI-5), sleep medication use (PSQI-6), and daytime dysfunction (PSQI-7). Each component is scored between 0 and 3 points. The total score of the scale is obtained by summing the scores of all subscales. The total score of the scale ranges from 0 to 21. If the

total score is below 5, it indicates good sleep quality, and equal or above 5 indicates poor sleep quality [25].

Statistical analysis

IBM SPSS software (Version 22.0 for Windows, SPSS Inc. NY, USA) was used for statistical analysis. Categorical variables were presented as frequency (N) and percentage (%), and continuous variables were expressed as median (M) and interquartile range (IQR). Normal distribution of the obtained data was assessed using visual and analytical methods. Non-parametric statistical methods were chosen as the data did not show normal distribution. A Mann–Whitney U test was used for comparison of independent variables. Statistical significance level was accepted as $P<0.05$.

The effect size (ES) was calculated to determine the clinical significance of the statistical results. The effect size was calculated using the formula "$r=z/\sqrt{N}$". The z score of the Mann Whitney *U* test was used for the calculation. The ES value was accepted as 0.1 to 0.3 "small", 0.3 to 0.5 "medium", and > 0.5 "large" [26].

G*Power 3.1.9.4 software (Heinrich-Heine-Universität Düsseldorf) was used for the power analysis. When the difference between the musculoskeletal pain of the participants with good and bad sleep quality was considered, the power of the study with 221 participants at 0.495 effect size was found to be 0.97 (power alpha=0.05). Evaluation results of individuals with missing data were not included in the analysis.

Results

Two-hundred thirty-three students filled out the online form, and 12 of these were excluded due to missing answers; thus, analyses of the answers of 221 students were done. Descriptive characteristics, daily smart mobile device usage times, and sleep quality scores of the students are shown in Table 1. Ninety-seven (43.89%) of the students participating in the study reported that they exercised regularly during the pandemic period, and they generally performed stretching and strengthening exercises and walking. Daily smart mobile device use time of 72 (32.6%) of the students was over 5 h. The sleep quality of 127 (57.5%) of the students was found to be poor. It was determined that no differences in terms of age, height, weight averages and gender distributions were found between the students with and without regular exercise habits, using mobile devices for more than 5 h and for 5 h or less, and with poor and good sleep quality ($P>0.05$).

Subjective sleep quality, sleep latency, and total PSQI scores of those who exercised regularly were significantly lower than those who did not exercise regularly ($P<0.001$, $P=0.005$, and $P=0.005$, respectively). Subjective sleep quality and sleep latency scores of those who used smart mobile devices more than 5 h a day were significantly higher than those who used less than 5 h a day ($P=0.002$ and $P=0.018$, respectively). However, the effect sizes were small (Table 2).

It was found that those with good and bad sleep quality had a significant difference in neck, right shoulder, upper back, waist and right wrist pain ($P=0.001$, $P=0.043$, $P=0.002$, $P<0.001$, and $P=0.014$, respectively). In addition, a significant difference was found between total CMDQ scores ($P<0.001$). However, the effect sizes were small (Table 3).

Table 1: Demographic features, exercise habits, mobile device use time, and sleep quality of the students (n=221)

	Mean (SD)
Age (years)	20.11 (1.64)
Height (cm)	164.48 (17.7)
Weight (kg)	61.16 (12.44)
	n (%)
Gender	
Female	187 (84.6)
Male	34 (15.4)
Exercise habit	
Exercising regularly	97 (43.9)
No exercising regularly	124 (56.1)
Daily smart mobile device use time	
≤5 hours	149 (67.4)
>5 hours	72 (32.6)
Sleep quality	
Good (PSQI total score <5)	94 (42.5)
Bad (PSQI total score ≥5)	127 (57.5)

SD: standard deviation, PSQI: Pittsburgh Sleep Quality Index

Table 2: Sleep quality based on regular exercise and daily mobile device usage time

	Exercising regularly (n=97) Median (IQR)	No exercising regularly (n=124) Median (IQR)	*P*-value	ES	Daily mobile device usage ≤5 hours (n=149) Median (IQR)	Daily mobile device usage >5 hours (n=72) Median (IQR)	*P*-value	ES
PSQI 1	1 (1)	1 (1)	<0.001*	0.24	1 (1)	2 (1)	0.002*	0.2
PSQI 2	1 (2)	2 (1)	0.005*	0.18	1 (2)	2 (1.75)	0.018*	0.15
PSQI 3	0 (0)	0 (0)	0.543	0.04	0 (0)	0 (0)	0.850	0.01
PSQI 4	0 (0)	0 (0)			0 (0)	0 (0)		
PSQI 5	1 (0)	1 (0)	0.650	0.03	1 (0)	1 (0)	0.763	0.02
PSQI 6	0 (0)	0 (0)	0.207	0.08	0 (0)	0 (0)	0.160	0.09
PSQI 7	1 (1)	1 (2)	0.414	0.05	1 (2)	1 (2)	0.961	0
PSQI total	4 (3.5)	6 (4)	0.005*	0.18	5 (4)	6 (4)	0.832	0.01

* *P*-value<0.05, PSQI: Pittsburgh Sleep Quality Index, ES: effect size, M: median, IQR: interquartile range

Table 3: Musculoskeletal discomforts of students with good or bad sleep quality

	PSQI score <5 (n=94)	PSQI score ≥5 (n=127)	*P*-value	ES
	Median (IQR)	Median (IQR)		
Neck	1.5 (3)	3 (14)	0.001*	0.22
Right shoulder	0 (1.5)	0 (6)	0.043*	0.13
Left shoulder	0 (1.5)	0 (3)	0.054	0.12
Upper back	1.5 (3.5)	3.5 (31.5)	0.002*	0.21
Right upper arm	0 (0)	0 (0)	0.681	0.02
Left upper arm	0 (0)	0 (0)	0.315	0.06
Waist	1.5 (3.5)	3 (20)	<0.001*	0.27
Right forearm	0 (0)	0 (0)	0.694	0.02
Left forearm	0 (0)	0 (0)	0.287	0.07
Right wrist	0 (0)	0 (1.5)	0.014*	0.16
Left wrist	0 (0)	0 (0)	0.736	0.02
Hip	0 (1.5)	0 (3)	0.067	0.12
Right thigh	0 (1.5)	0 (1.5)	0.763	0.02
Left thigh	0 (1.5)	0 (1.5)	0.730	0.02
Right knee	0 (0)	0 (0)	0.972	0
Left knee	0 (0.38)	0 (0)	0.985	0
Right lower leg	0 (0)	0 (0)	0.264	0.07
Left lower leg	0 (0)	0 (0)	0.505	0.04
Right foot	0 (0)	0 (0)	0.198	0.08
Left foot	0 (0)	0 (0)	0.238	0.07
CMDQ total score	11.75 (27.75)	42 (115.5)	<0.001*	0.28

* *P*-value<0.05, PSQI: Pittsburgh Sleep Quality Index, CMDQ: Cornell Musculoskeletal Discomfort Questionnaires, ES: effect size, M: median, IQR: interquartile range

Discussion

In the study, we planned to examine the sleep quality and musculoskeletal system pain in distance education students during the pandemic period. We determined that the sleep quality of most of the students was bad, and those who were physically inactive and had more screen time had worse sleep quality. In addition, we found that those with poor sleep quality had more musculoskeletal discomfort.

It has been reported that sleep quality decreased in the general population [27–29] and university students [11,12,30] during the pandemic period. In the current study, the sleep quality of most of the participants was found to be poor. We think that the change in daily routines during the pandemic period and the increase in screen usage time and physical inactivity that occurred because of the transition to distance education may be effective in negatively affecting sleep quality.

Marelli et al. [12] stated that sleep latency also increased in university students during the pandemic period. According to the findings of our study, a reduction in increased screen usage time and low physical activity level during the pandemic period may be effective in increasing sleep latency.

It has been recommended to establish a sleep routine, maintain a certain level of physical activity, and be exposed to more daylight in order to reduce negative effects on sleep during the pandemic period [31]. Diniz et al. [32] also reported that decreased physical activity during the pandemic period adversely affected sleep pattern. Nixon et al. [33] stated that physical activity shortens sleep latency. Our study findings also show that those who exercise regularly fall asleep in a shorter time. Subjective sleep quality and total PSQI scores were also higher in those who did not exercise regularly. The lack of difference in other sleep scores such as sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction suggests that sleep effects were limited during the pandemic period due to the fact that the participants of the study were young and healthy students. The fact that sleep quality was found to be higher in those who have regular exercise habits in our study shows that distance education students can be protected from negative effects related to sleep by exercising.

It has been reported that screen use time increased in university students during the pandemic period and this situation is associated with poor sleep [34]. In the current study, 32.6% of the students were using smart mobile devices for more than 5 h. Although smart mobile devices make life easier in terms of access to information, communication and ensuring the continuity of education during the pandemic, it has been reported that the types of mobile devices and excessive use were risk factors for musculoskeletal injuries [35]. Cellini et al. [11] found that use of digital media before going to bed negatively affected sleep latency. Huang et al. [36] reported that inappropriate content on websites that some phone users browse before going to bed may cause users to experience tension and excitement thus causing them to have difficulty falling asleep in some physiological and psychological ways and that more than one variable may be effective on sleep. In the current study, long-term use of mobile devices led to an increase in subjective sleep quality score and sleep latency but did not affect other sleep-related components. The fact that our study participants were young adults and did not have any co-morbid disease may be a reason why other sleep-related components were not affected. The fact that sleep quality is worse in those who use smart mobile devices for more than 5 h suggests that correct adjustment of the screen time during the distance education period is necessary for sleep quality.

Many studies suggesting that increasing sleep problems and psychological problems during the pandemic period may be related to each other are available [12,13]. However, less attention has been paid to the relationship between sleep problems and physical health during the pandemic period. It has been reported that poor sleep quality is associated with low back and neck pain in adolescents [37]. Karatel et al. [38] reported that musculoskeletal pain and sleep quality were associated in Turkey during the pandemic period. In our study, the fact that those with poor sleep quality had more discomfort in the whole spine, especially in the neck, upper back, and waist regions, may be due to their long periods in inappropriate postures during the day due to distance education. However, greater discomfort, especially in the right wrist and shoulder, may be associated with increased use of the right extremities. The fact that the musculoskeletal pain of those with poor sleep quality was a more common finding in our study and suggests that the measures taken to increase the sleep quality of the distance education students would be beneficial for preventing the development of chronic musculoskeletal pain.

Limitations

Our study is important in terms of revealing the effect of sleep quality on musculoskeletal pain in university students receiving distance education during the pandemic period. However, not evaluating physical activity in detail and not questioning students' physical activity, sleep quality, and pain status before the start of the pandemic can be counted as limitations. In future studies, it will be useful to examine the effects of practices that lead to an increase in physical activity and improvement in sleep quality in distance education students.

Conclusion

In conclusion, the results of our study show that not doing regular exercise and using smart mobile devices for a long time during the pandemic process in which university students continue their distance education negatively affect sleep quality. Students with poor sleep quality also had more musculoskeletal pain, especially in the neck, back and waist. We think that it will be beneficial for students to reduce their screen time and participate in regular physical activity so that they do not encounter health problems related to sleep problems and do not become individuals with chronic pain in the future.

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A case of spontaneous ovarian malignant neoplasm rupture and life-threatening massive intra-abdominal bleeding

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Abstract

Although ovarian cancer is the second most common gynecological cancer, it is the most common gynecological malignancy that causes death. Approximately 75% of the patients are diagnosed at an advanced stage, and high-grade serous-type ovarian cancer is detected in most of these patients. The final pathology result in our case was high-grade serous ovarian carcinoma. Our patient, 39 years old, applied to our emergency department with complaints of inability to urinate for three days and new onset abdominal pain. We were consulted because of detection of an 11 cm solid mass and globe vesicle in the pelvic region detected on the computed tomography (CT) taken in the emergency department. The patient's initial hemoglobin value was 11.2 g/dL and the beta-human chorionic gonadotropin (ß-HCG) value was negative. During the follow-up, the patient's hemoglobin values were 9.2 and then decreased to 8.6, 8.1, and 6.5 g/dL after which hypotensive shock developed in the patient. The patient was taken for an emergency laparotomy. Intra-operatively, 1500 mL of intra-abdominal hemorrhagic fluid and diffuse tumor fragments were observed. In the right adnexal area, approximately 11 cm of ruptured tumor tissue, which may originate from the ovary or uterus, was observed. It was observed that the Douglas pouch and uterine, internal iliac , and some parts of the external iliac arteries were extensively invaded by the tumor and active bleeding occurred. Total Abdominal Hysterectomy + Bilateral Salpingo-Oopherectomy (TAH+BSO) was performed on the patient. Additional surgical intervention could not be performed because the patient had extensive vascular tumor invasion, heavy bleeding, and was in hypotensive shock. Six anti-bleeding sponges were placed on intra-abdominal bleeding areas. In addition, packing was applied to the patient by placing four sterile compresses and soft drains inside the abdomen. Tranexamic acid was administered to the patient, and six units of red blood cell suspension and four units of fresh frozen plasma were transfused. The patient was transferred by ambulance to a higher institution, which is a gynecological oncology center, for follow-up, treatment, and complementary surgery. In this case, we aimed to draw attention to a rare case of ovarian malignancy rupture and hypotensive shock.

Keywords: hypovolemic shock, ovarian tumor, serous carcinoma

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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Introduction

Rupture of gynecological tumors can result in acute abdomen. Bleeding may occur depending on the tumor size and rupture site. Peritonitis and acute abdomen findings may be caused by bleeding. The literature presents rare cases of rupture and acute abdomen caused by teratomas [1,2]. Ovarian epithelial tumors are among the leading causes of death among gynecological cancer patients [3]. Ovarian cancers, on the other hand, take fifth place among cancer-related deaths [4]. Epithelial tumors have an important place in malignant neoplasms of the ovary. Among the epithelial tumors, serous and mucinous cystadenocarcinomas have an important place. The rupture of epithelial tumors is very rare and usually associated with surgery manipulation [5]. In rare cases, spontaneous tumor rupture has been reported in patients who were pregnant and using anticoagulants [6,7]. In addition, three cases of rupture of ovarian germ cell tumors (two cases of teratoma and one case of yolk sac tumor) and one case of rupture of benign dermoid cysts due to blunt abdominal trauma have been reported [8–11]. Our case is one of spontaneous rupture and serous carcinoma of the ovary.

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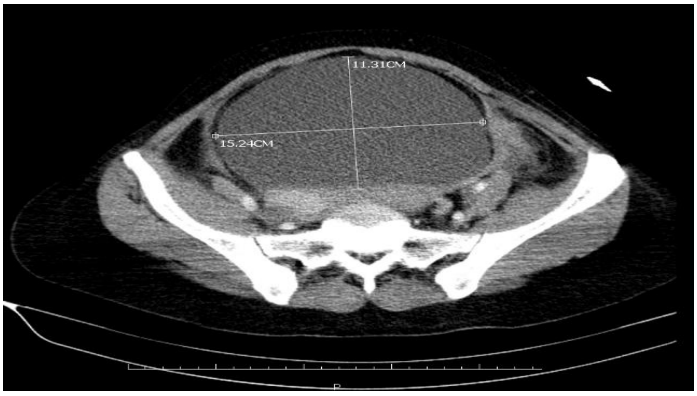
Case presentation

Our patient, 39 years old, applied to our emergency service with complaints of inability to urinate for three days and new onset abdominal pain. Our patient did not have any co-morbid conditions and did not have a history of drug use. No anticoagulant use, trauma, or pregnancy was reported. On the computed tomography (CT) taken in the emergency room, a solid mass of 11 cm and a globe vesicle were detected in the pelvic region (Figure 1).

Figure 1: Glop vesical



After the urinary catheter was inserted in the emergency room, the patient's abdominal pain gradually increased. In addition, a rapid decrease was observed in the hemogram values of the patient after urinary catheter insertion. The patient's vital signs were aggressively impaired. We were consulted after the patient was found to have an 11 cm solid mass, which may have originated from the ovary. During the physical examination of the patient, the entire abdomen was tender, and rebound and defense were detected. Based on the pelvic examination, the cervix was normal, and the Douglas cavity was found to be involved with tumor tissue. Abdominal ultrasonography (USG) and transvaginal ultrasonography (TV-USG) revealed diffuse fluid in the hepatorenal and splenorenal areas (Figure 2). A 11 x 10 x 10 cm solid mass formation with irregular borders was observed in the pelvic region (Figure 3).

Figure 2: Hepatorenal fluid

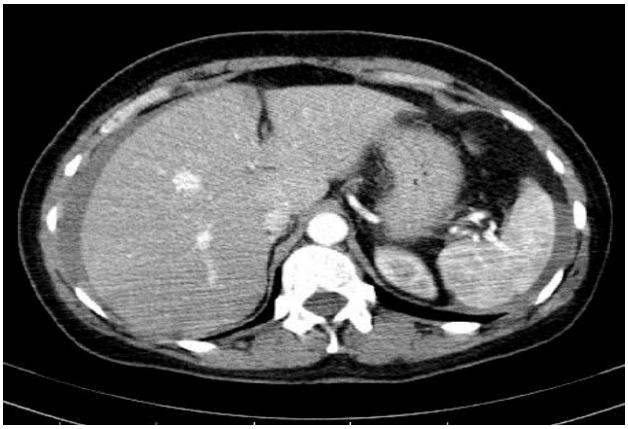
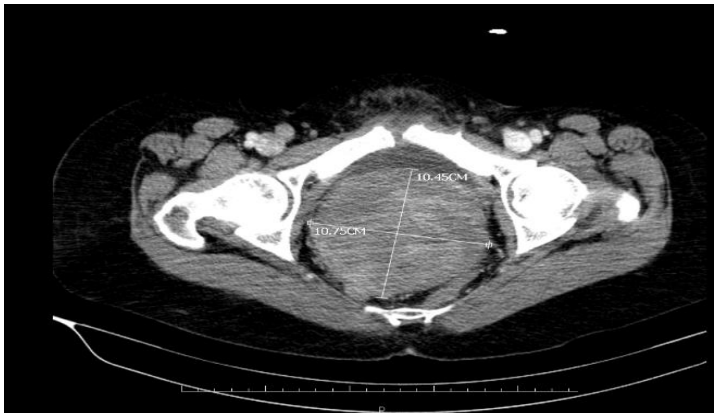


Figure 3: Tumor



In addition, widespread free fluid was observed in the pelvic region. The hemoglobin value at the time of the patient's emergency admission was 11.2 g/dL, and the beta-human chorionic gonadotropin (ß-HCG) value was negative. In the follow-up, the patient's hemoglobin values were 9.2, and then decreased dB to 8.6, 8.1, and 6.5 g/dL after which the patient developed hypotensive shock. The patient underwent an emergency laparotomy. The hemoglobin value measured at the beginning of the operation was 5.5 g/dL. Intra-operatively, 1500 mL of intra-abdominal hemorrhagic fluid and diffuse tumor fragments were observed. In the right adnexal area, approximately 11 cm of ruptured tumor tissue, which may have originated from the ovary or uterus, was observed. The Douglas pouch and uterine, internal iliac, and some parts of the external iliac arteries were observed to be extensively invaded by the tumor and actively bleeding. Total Abdominal Hysterectomy + Bilateral Salpingo-Oopherectomy (TAH+BSO) was performed on the patient. Additional surgery could not be performed because the patient had extensive vascular tumor invasion, massive bleeding, and hypotensive shock. Six bleeding stopper sponges were placed in the intra-abdominal bleeding areas. In addition, packing was applied to the patient by placing four sterile compresses and soft drains inside the abdomen. Tranexamic acid was administered to the patient, and six units of red blood cell suspension and four units of fresh frozen plasma were transfused. The patient was transferred by ambulance to a higher institution with a gynecological oncology center in terms of follow-up, treatment, and complementary surgery. When the patient's abdomen was opened again, it was observed that the bleeding had stopped. The patient underwent omentectomy, appendectomy, bilateral external iliac, and obturator and para-aortic lymph node dissection as complementary surgery. As a result of the pathology examined in our hospital, it was reported that the macroscopic image could be serous carcinoma of the ovary and/or endometrial papillary serous carcinoma.

Later, the diagnosis of serous carcinoma of the ovary was made based on immunohistochemical staining for the definitive diagnosis. Our patient died six months after the definitive diagnosis was made.

Discussion

Patients with food impaction often have underlying esophageal pathology. The risk is increased in people with previous gastrointestinal surgery [4]. The fact that most of the patients with esophageal bezoars have a history of Nissen fundoplication surgery showed that this surgical intervention,

which is widely used in the treatment of hiatal hernia and reflux esophagitis, paves the way for esophageal bezoars [2]. Esophageal bezoars are extremely rare, and only a few case reports have described esophageal bezoars. There are very few case reports specifically seen after fundoplication [3].

Patients with bezoars in the gastrointestinal tract are usually easily diagnosed. CT is helpful in diagnosis. However, the gold standard for diagnosis is endoscopy for upper gastrointestinal bezoars [4]. CT is the most commonly used imaging method in the diagnosis of bezoars and is very useful for definitive diagnosis in patients with intestinal obstruction [5]. However, endoscopy remains the gold standard for research because it can directly visualize and treat the condition [6]. In our case, we first determined the location of the bezoar via a CT scan. We then removed the bezoar with endoscopy.

Foreign bodies and bezoars in the esophagus should be removed within 24 hours because delays in the removal may increase the risk of complications. These complications include perforation, obstruction, and narrowing [4]. We removed the bezoar by endoscopy at the sixth hour of hospitalization in our case. The procedure was completed without complications.

Bezoar removal in the esophagus is most commonly done by pushing food into the stomach or mechanically removing it. As in our patient, it may be difficult to push the bezoar into the stomach in patients who have undergone fundoplication. The use of proteolytic enzymes is also not recommended due to the risk of perforation. Mechanical dissection is recommended to safely treat esophageal bezoars [7].

The ultimate goal of bezoar treatment is removal of the mass and prevention of its recurrence. The treatment options available for this condition should be well evaluated. The minimal benefits to patient should be considered [1]. Surgery is a difficult decision for esophageal bezoars. Rather, minimally invasive interventions with endoscopic procedures are preferred.

Conclusion

Esophageal bezoars should be considered in patients with a history of Nissen fundoplication operation when gastrointestinal obstruction is encountered with nausea, vomiting, and a feeling of obstruction in the retrosternal region. In such cases, CT may be first requested to support the diagnosis. Clearer imaging can be done with endoscopy. Endoscopy should not be delayed after a history of fundoplication and a pre-diagnosis of bezoars. More importantly, it should not be forgotten that it can be treated with endoscopy. It is safer to disintegrate the bezoar rather than push it into the stomach in patients with a history of fundoplication operation.

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